AMINOALKYL-PYRAZINONES AND -PYRIDONES AS THROMBIN INHIBITORS

The present invention relates to aminoalkyl-pyrazinones and -pyridones having an antithrombotic effect and their prodrugs useful as anticoagulants for the treatment or prophylaxis of thrombin related diseases.

Venous and arterial thromboembolism may cause pulmonary embolism, myocardial infarction and ischaemic stroke and hence are a major cause for morbidity and mortality. Therefore, significant efforts have been made to find effective antithrombotic therapies. The list of established drugs for the prevention of thrombus formation and embolisation include low molecular weight heparins, hirudin and its derivatives, aspirin, thienopyridine-type ADP receptor antagonists and glycoprotein IIb/IIIa receptor antagonists, as well as vitamin K antagonists. Several limitations caused some these therapies being of only limited use or leading to severe implications. These treatments have limited use because of severe side effects. These limitations in current therapies have stimulated the search for new and more efficient anticoagulants.

Thrombin is a serine protease present in blood plasma in the form of its precursor, prothrombin (Mann, K.G., *Biochemistry and physiology of blood coagulation, Thromb. Haemost.* 1999, 82, 165-74) and plays a central role in the mechanism of blood coagulation by converting the soluble plasma protein fibrinogen into the insoluble fibrin which forms a clot. In addition, thrombin transforms coagulation factor XII to factor VIIIa which covalently cross-links the fibrin strands. Thrombin is responsible for a variety of cellular actions mediated by binding to specific protease-activated receptors (O'Brien, P.J. et al. *Protease activated receptors: theme and variations. Oncogene* 2001, 20, 1570-81). In addition, thrombin is one of the most potent stimulators of platelet aggregation and also a potent mitogen for vascular muscle cells.

Due to its multiple physiological actions in the context of blood coagulation, thrombin is a suitable target for drug discovery and development.

3-Amino-2-pyridone and 5-amino-6-pyrimidone acetamide templates are described as effective surrogates for the glycylproline dipeptide backbone of inhibitors of human leukocyte elastase (Brown, F.J., et al., J. Med.Chem, 1994, 37, 1259-61).

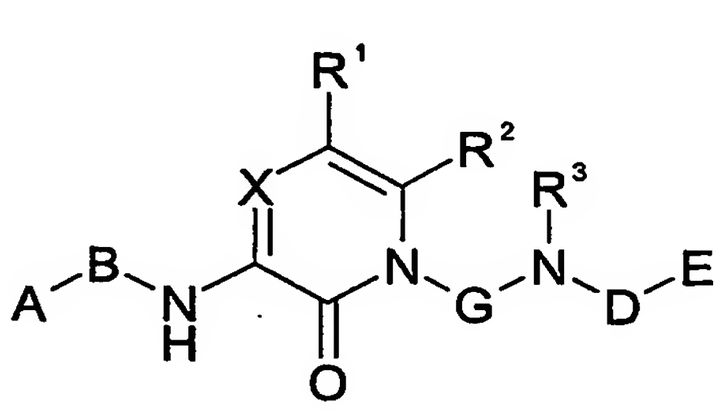
In US5668289 (1997), WO9831670 (1998), WO9730708 (1997) and WO9701338 (1997) several sulfonylated pyridone acetamides are described to be potent and selective inhibitors of thrombin. Further pyridone acetamides are described in WO0032574 (2000) and WO9926926 (1999).

In WO9740024 (1997) Pyrazinone acetamides are described to be potent inhibitors of thrombin. Structural variations led to further pyrazinone acetamides published in WO9911267 (1999), WO9961442 (1999), WO9959591 (1999), WO0026210 (2000). EP-0997474 discloses further pyrazinone acetamides as thrombin inhibitors. A further series of Pyridones and Pyrazinones described to show activity as thrombin inhibitors is comprised by US 2003/0092679.

However, the compounds described so far do not satisfy the demanding needs for effective antithrombotic agents, anticoagulants or thrombin inhibitors.

Thus, the object of the present invention is to provide novel and selective compounds which can overcome at least some of the draw backs of compounds considered state-of-the-art.

Accordingly, the present invention provides compounds of formula (I):



(I)

or a pharmaceutically acceptable salt thereof, wherein:

R^1 is hydrogen;
halogen; or
C_{1-4} alkyl, optionally substituted with one or more fluoro;

R^2 is hydrogen;
halogen;
C_{1-6} alkyl, optionally substituted with one or more fluoro;
C_{3-6} cycloalkyl; or
$O\text{-}C_{1-4}$ alkyl;

R^3 is hydrogen;
C_{1-4} alkyl; or
C_{3-6} cycloalkyl;

A is A^1, wherein A^1 is selected from the group consisting of:
phenyl;
naphthyl;
heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, $-S(O_2)-$, -N=, -N(O)= and $-N(R^4)-$; and
heterobicycles containing up to 6 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, $-S(O_2)-$, -N=, -N(O)= and $-N(R^4)-$;
wherein A^1 is optionally substituted with one or independently from each other more of
A^2;
A^3;
halogen;
$-N(R^5R^6)$;
-OH;
=O, where the ring is at least partially saturated;
C_{3-6} cycloalkyl;
$-COOR^7$; or
$-CONR^8R^9$;
$-S(O)_2NR^{8a}R^{9a}$

and wherein R^4, R^5, R^6 are independently selected from the group consisting of R^{7a}, $-C(O)-R^{7a}$, $-C(O)O-R^{7a}$, $-C(O)NR^{7a}R^{7b}$, $-S(O)_2NR^{7a}R^{7b}$, and $S(O)_2-R^{7a}$;
and wherein R^7, R^{7a}, R^{7b}, R^8, R^{8a}, R^9, R^{9a} are independently hydrogen or C_{1-4} alkyl, wherein each C_{1-4} alkyl is optionally substituted with one or more

substituents independently selected from the group consisting of -COOH; -OH; -NH_2; -NH-C_{1-4} alkyl; -N(C_{1-4} alkyl)$_2$; and C_{3-6} cycloalkyl;

Optionally R^4 is a bond to directly attach A to B;

A^2 is selected from the group consisting of A^4, -O-A^4 and -N(R^{10})-A^4,

wherein A^4 is phenyl or a heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, -N=, -N(O)= and -N(R^{11})-; wherein A^4 is optionally substituted with one or independently from each other more of

fluoro;

chloro;

-N($R^{12}R^{13}$)

C_{1-4} alkyl or -O-C_{1-4} alkyl, both optionally substituted with one or independently from each other more of fluoro or -N($R^{14}R^{15}$);

and wherein R^{10}, R^{12}, R^{13}, R^{14}, R^{15} are independently hydrogen or C_{1-4} alkyl;

and wherein R^{11} is selected from the group consisting of hydrogen, C_{1-4} alkyl and -C(O)-C_{1-4} alkyl;

A^3 is selected from the group consisting of C_{1-6} alkyl, -O-C_{1-6} alkyl and -N(R^{16})-C_{1-6} alkyl, wherein the C_{1-6} alkyl group is optionally substituted with one or independently from each other more of

fluoro;

-N($R^{17}R^{18}$);

A^5;

and/or A^3 is optionally interrupted with one or more oxygen;

and wherein R^{16}, R^{17}, R^{18} are independently hydrogen or C_{1-4}alkyl;

A^5 is phenyl or a heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, -N=, -N(O)= and -N(R^{19})-; wherein A^5 is optionally substituted with one or independently from each other more of

fluoro;

chloro;

-N($R^{20}R^{21}$)

C_{1-4} alkyl or -O-C_{1-4} alkyl, both optionally substituted with one or independently from each other more of fluoro or -N($R^{22}R^{23}$);
and wherein R^{19} is selected from the group consisting of hydrogen, C_{1-4} alkyl and -C(O)-C_{1-4} alkyl;
and wherein R^{20}, R^{21}, R^{22}, R^{23} are independently hydrogen or C_{1-4} alkyl;

B is selected from the group consisting of -Y-Z-; -Y-Z-C(O)-; -Y-Z-O-C(O)-; -Y-Z-$S(O)_2$-; and -Y-Z-NH-C(O)- wherein

Y is a bond, -O-, -S-, -N(R^{24})-, -N(R^{25})-C(O)-, -C(O)-N(R^{26})-, or -C(O)-;

Z is C_{1-6} alkyl,

optionally interrupted with oxygen, sulfur or -N(R^{27})-

and/or optionally substituted with one or independently from each other more of

halogen;

C_{3-6} cycloalkyl;

-$COOR^{28}$;

-$CON(R^{29}R^{30})$

and/or optionally one chain carbon forms part of a C_{3-6} cycloalkyl;

and wherein R^{24}, R^{25}, R^{26}, R^{27}, R^{28}, R^{29}, R^{30} are independently

hydrogen; or

C_{1-4} alkyl, optionally substituted with -$COOR^{31}$ or -$CON(R^{32}R^{33})$

wherein R^{31}, R^{32}, R^{33} are independently hydrogen or C_{1-4} alkyl;

X is =$C(R^{34})$- or =N-, wherein R^{34} is

hydrogen;

C_{1-6} alkyl, optionally substituted with one or more fluoro; or

-$S(O)_2R^{35}$, wherein R^{35} is selected from the group consisting of X^1, C_{1-6} alkyl, and -C_{1-6} alkyl-X^1; wherein R^{35} is optionally substituted with one or independently from each other more of

fluoro;

chloro;

C_{1-4} alkyl; or

-O-C_{1-4} alkyl;

X^1 is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, -N=, -N(O)= and -N(R^{36})-; and wherein R^{36} is selected from the group consisting of hydrogen, C_{1-4} alkyl and -C(O)-C_{1-4} alkyl;

G is -CH(R^{37})-C($R^{38}R^{39}$)-;

-CH(R^{37})-C($R^{38}R^{39}$)-C($R^{40}R^{41}$)-;

wherein R^{37}, R^{38}, R^{39}, R^{40}, R^{41} are independently

hydrogen;

C_{1-4} alkyl, optionally substituted with one or more fluoro;

C_{3-6} cycloalkyl, optionally substituted with one or more fluoro;

or R^{38} and R^{39} or R^{40} and R^{41} form together C_{3-6} cycloalkyl, optionally substituted with one or more fluoro, -OH, C_{1-4} alkyl;

or R^{37} and R^{38} or R^{38} and R^{40} form together C_{3-6} cycloalkyl, optionally substituted with one or more fluoro, -OH, C_{1-4} alkyl;

D is C_{1-6} alkyl,

optionally interrupted with oxygen, sulfur or -N(R^{42})-

and/or optionally substituted with halogen, C_{3-6} cycloalkyl;

and/or optionally one chain carbon or two vicinal carbons form part of a C_{3-6} cycloalkyl, wherein R^{42} is selected from the group consisting of hydrogen, C_{1-4} alkyl, C_{3-6} caycloalkyl and -C(O)-C_{1-4} alkyl;

E is E^1, wherein E^1 is selected from the group consisting of

phenyl;

naphthyl;

heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, -N=, -N(O)= and -N(R^{43})-; and

heterobicycle containing up to 6 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, -N=, -N(O)= and -N(R^{44})-;

wherein E^1 is optionally substituted with one or independently from each other more of

E^2;

E^3;

halogen;

$-N(R^{45}R^{46})$;

-OH;

=O, where the ring is at least partially saturated;

C_{3-6} cycloalkyl;

$-COOR^{47}$; or

$-CONR^{48}R^{49}$;

$-S(O)_2NR^{48a}R^{49a}$;

and wherein R^{43}, R^{44}, R^{45}, R^{46} are independently selected from the group consisting of hydrogen;

C_{1-4} alkyl optionally substituted with -OH;

and $-C(O)-C_{1-4}$ alkyl optionally substituted with -OH;

and wherein R^{47}, R^{48}, R^{48a}, R^{49}, R^{49a} are independently hydrogen or C_{1-4} alkyl, optionally substituted with -OH;

E^2 is selected from the group consisting of E^4, $-C(O)-E^4$, $-O-E^4$ and $-N(R^{50})-E^4$,

wherein E^4 is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, $-S(O_2)-$, -N=, -N(O)= and $-N(R^{51})-$; wherein E^4 is optionally substituted with one or independently from each other more of

fluoro;

chloro;

cyano;

=O, where the ring is at least partially saturated;

$-N(R^{52}R^{53})$;

C_{1-4} alkyl; or

$-O-C_{1-4}$ alkyl;

and wherein R^{50}, R^{52}, R^{53} are independently hydrogen or C_{1-4} alkyl, optionally substituted with -OH;

and wherein R^{51} is selected from the group consisting of

hydrogen;

C_{1-4} alkyl, optionally substituted with -OH; and

$-C(O)-C_{1-4}$ alkyl, optionally substituted with -OH;

E^3 is selected from the group consisting of C_{1-6} alkyl, -O-C_{1-6} alkyl; -N(R^{54})-C_{1-6} alkyl, wherein E^3 is optionally substituted with one or independently from each other more of

fluoro;

-N($R^{55}R^{56}$);

E^5;

and/or E^3 is optionally interrupted with one or more oxygen;

and wherein R^{54}, R^{55}, R^{56} are independently hydrogen or C_{1-4}alkyl, optionally substituted with -OH;

E^5 is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, -S(O_2)-, -N=, -N(O)= and -N(R^{57})-; wherein E^5 is optionally substituted with one or independently from each other more of

fluoro;

chloro;

cyano;

=O, where the ring is at least partially saturated;

-N($R^{58}R^{59}$);

C_{1-4} alkyl or

-O-C_{1-4} alkyl;

and wherein R^{57} is independently selected from the group consisting of hydrogen;

C_{1-4}alkyl, optionally substituted with -OH; and

-C(O)-C_{1-4} alkyl, optionally substituted with -OH;

and wherein R^{58}, R^{59} are independently hydrogen or C_{1-4} alkyl, optionally substituted with -OH.

Within the meaning of the present invention the terms are used as follows:

"Alkyl" means a straight-chain or branched carbon chain that may contain double or triple bonds.

"C_{1-4} Alkyl" means an alkyl chain having 1 - 4 carbon atoms, e.g. at the end of a molecule methyl, ethyl, -CH=CH_2, -C≡CH, n-propyl, isopropyl, -CH=CH-CH_3, -CH_2-CH=CH_2, n-butyl, isobutyl, -CH=CH-CH_2-CH_3, -CH=CH-CH=CH_2, sec-butyl tert-butyl or

amidst, e.g. $-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH(CH_3)-$, $-C(CH_2)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-CH(CH_3)_2-$.

"C_{1-6} Alkyl" means an alkyl chain having 1 - 6 carbon atoms, e.g. C_{1-4} Alkyl, methyl, ethyl, $-CH=CH_2$, $-C\equiv CH$, n-propyl, isopropyl, $-CH=CH-CH_3$, $-CH_2-CH=CH_2$, n-butyl, isobutyl, $-CH=CH-CH_2-CH_3$, $-CH=CH-CH=CH_2$, sec-butyl tert-butyl, n-pentane, n-hexane, or amidst, e.g. $-CH_2-$, $-CH_2-CH_2-$, -CH=CH-, $-CH(CH_3)-$, $-C(CH_2)-$, $-CH_2-CH_2-CH_2-$, $-CH(C_2H_5)-$, $-CH(CH_3)_2-$.

An alkyl chain "interrupted" with a heteroatom means that between two carbon atoms or at the end of the alkyl chain a heteroatom, e.g. nitrogen, oxygen or sulfur, is added. This includes for example C_{1-4} alkyl interrupted by an oxygen atom, e.g. $-CH_2-OH$, $-CH_2-O-CH_3$, CH_2-CH_2-OH, $-C_3H_6-OCH_3$.

Each hydrogen of a carbon or heteroatom of the alkyl chain or interrupted alkyl chain may be replaced by a substituent.

"C_{3-6} Cycloalkyl" means a cyclic alkyl chain having 3 - 6 carbon atoms, e.g. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl. Each hydrogen of a cycloalkyl carbon may be replaced by a substituent.

"Halogen" means fluoro, chloro, bromo and so called pseudo-halogens, i.e. -CN or -CNO.

"Heterocycle" means a cyclopentane, cyclohexane or cycloheptane ring that may contain up to the maximum number of double bonds (aromatic or non-aromatic ring which is fully, partially or un-saturated) wherein at least one carbon atom up to a maximum number of carbon atoms, as indicated, is replaced by a heteroatom ("containing" or "having" a heteroatom) and wherein the ring is linked to the rest of the molecule via a carbon or nitrogen atom. Examples for a heterocycle are furan, thiophene, pyrrole, pyrroline, imidazole, imidazoline, pyrazole, pyrazoline, oxazole, oxazoline, isoxazole, isoxazoline, thiazole, thiazoline, isothiazole, isothiazoline, thiadiazole, thiadiazoline, tetrahydrofuran, tetrahydrothiophene, pyrrolidine, imidazolidine, pyrazolidine, oxazolidine, isoxazolidine, thiazolidine, isothiazolidine, thiadiazolidine, sulfolane, pyran, dihydropyran, tetrahydropyran, imidazolidine, pyridine, pyridazine, pyrazine, pyrimidine, piperazine, piperidine, morpholine, tetrazole, triazole, triazolidine, tetrazolidine, azepine or homopiperazine.

"Heterobicycle" means a heterocycle which is condensed with phenyl or an additional heterocycle to form a bicyclic ring system. "Condensed" to form a bicyclic ring means that two rings are attached to each other by sharing two ring atoms. Examples for a heterobicycle are indole, indoline, benzofuran, benzothiophene, benzoxazole, benzisoxazole, benzothiazole, benzisothiazole, benzimidazole, benzimidazoline, quinoline, quinazoline, dihydroquinazoline, dihydroquinoline, isoquinoline, tetrahydroisoquinoline, dihydroisoquinoline, benzazepine, purine or pteridine.

Preferred compounds of the formula (I) are those compounds in which one or more of the residues contained therein have the meanings given below, with all combinations of preferred substituent definitions being a subject of the present invention. With respect to all preferred compounds of the formula (I) the present invention also includes all tautomeric and stereoisomeric forms and mixtures thereof in all ratios, and their pharmaceutically acceptable salts.

In preferred embodiments of the present invention, the substituents R^1 - R^3, A, B, X, G, D and E of the formula (I) independently from each other have the following meaning. Hence, one or more of the substituents R^1 - R^3, A, B, X, G, D and E can have the preferred or more preferred meanings given below.

R^1 is preferably hydrogen.

R^2 is preferably hydrogen hydrogen, chloro, $-CH_3$, $-CH_2-CH_3$, $-CH_2-CH_2-CH_3$, $-CH_2-CH_2-CH_2-CH_3$, $-CH_2F$, $-CHF_2$ or -CN.

R^3 is preferably hydrogen.

Preferably in A is A^1 phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, -S(O)-, $-S(O_2)-$, -N=, -N(O)= and $-N(R^4)-$, wherein R^4 has the meaning as indicated above.

More preferred, A^1 is selected from the group consisting of phenyl, pyridine, pyridine-N oxide, piperidine, morpholine, and pyrrolidine.

Preferably, R^4 is a bond, -$COOC_{1-4}$ alkyl, methyl, ethyl, 2-hydroxyethyl, -COOH, -CH_2-COOH, -CH_2-COO-C_{1-4} alkyl or cyclopropylmethyl and preferably, A^1 is optionally substituted with up to 4 F.

Preferably, B is -Y-Z-.

Preferably in B is Y preferably a bond, -O-, -NH-, -$S(O)_2$- or-C(O)-; and Z is preferably -$C(R^{60}R^{61})$- or -$C(R^{60}R^{61})$-$C(R^{62}R^{63})$-, wherein

R^{60}, R^{61}, R^{62}, R^{63} are independently hydrogen, -$C(O)NH_2$, -COOH, -CH_2-COOH, -CH_2-$C(O)NH_2$, fluoro, methyl, cyclopropyl or

R^{60} and R^{61} form a cyclopropyl ring or

R^{62} and R^{63} form a cyclopropyl ring or

R^{60} and R^{62} form a cyclopropyl or cyclobutyl ring.

Preferably, R^{60}, R^{61}, R^{62}, R^{63} are independently hydrogen, fluoro or -$C(O)NH_2$.

X is preferably =N-.

G is preferably -$CH(R^{64})$-$C(R^{65}R^{66})$-; wherein R^{64}, R^{65}, R^{66} are independently hydrogen, F, methyl, -CH_2F, -CHF_2, CF_3 or cyclopropyl or R^{65}, R^{66} form together cyclopropyl.

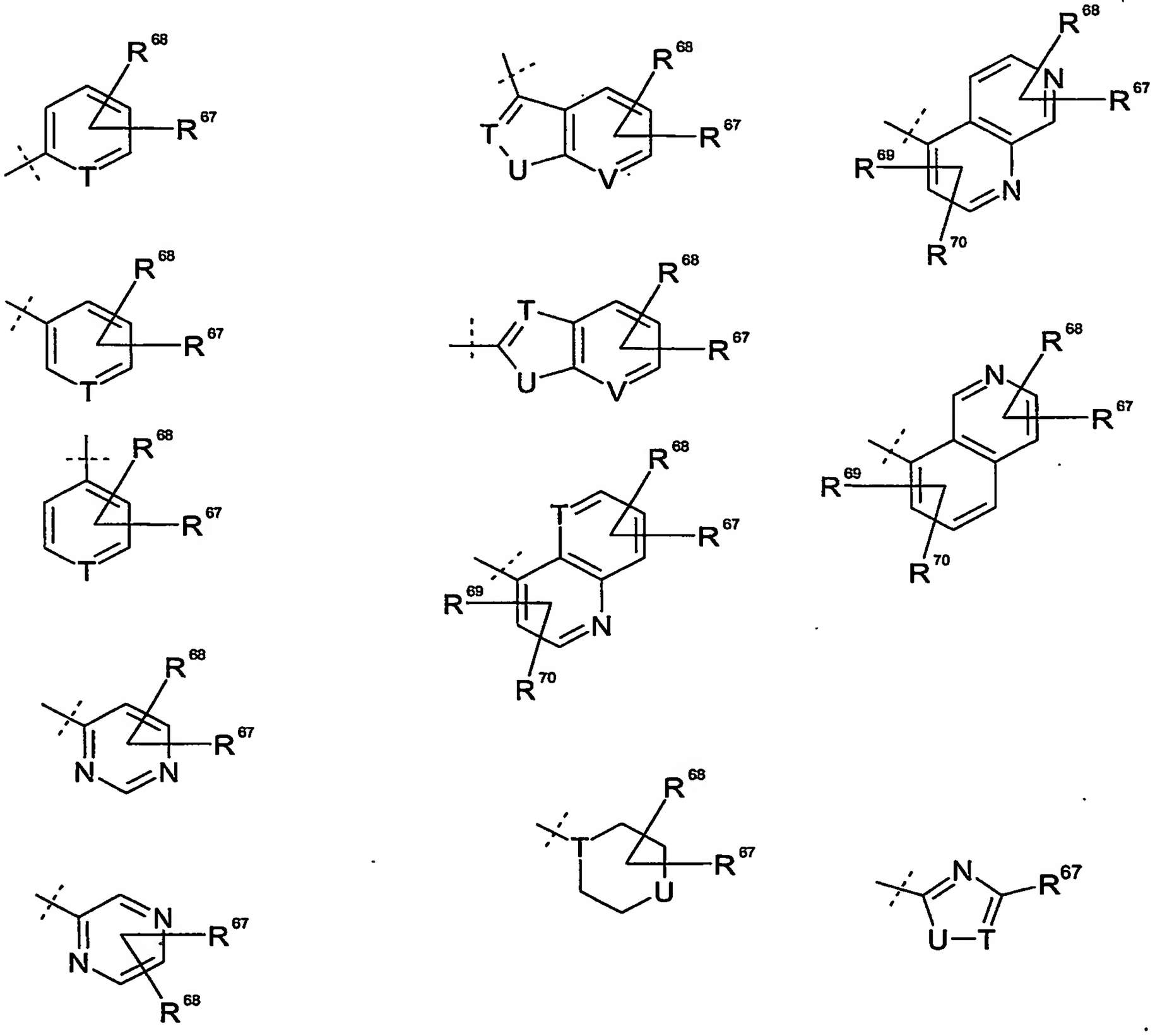
It is also preferred that G is -CH_2-CH_2-.

Preferably, D is -CH_2-, -CF_2-, -$CH(CH_3)$-, -$C(CH_3)_2$- or D^1-D^2, where D^1 and D^2 are independently -CH_2-, -CF_2-, -$CH(CH_3)$- or -$C(CH_3)_2$- and wherein D^2 is optionally -CH_2-NH-. More preferred D is -CH_2-, -$CH(CH_3)$-, -CH_2-CH_2-, -CH_2-CF_2 or -CH_2-CH_2-NH-.

Preferably, E is selected from the group consisting of phenyl; heterocycle containing up to three heteroatoms, which are the same or different and selected from the group consisting of -O-, -N=, -N(O)- and -NH-; and heterobicycle containing up to three heteroatoms, which are the same or different and selected from the group consisting of -O-, -N=, and -NH-; and wherein E is optionally substituted with up to two substituents which are the same or different and selected from the group consisting of CN, F, Cl, C_{1-4} alkyl, OH, O-C_{1-4} alkyl, NH_2, NH-C_{1-4} alkyl, N(C_{1-4} alkyl)$_2$, $C(O)NH_2$, C(O)NH-C_{1-4} alkyl,

and C(O)N(C_{1-4} alkyl)$_2$, wherein each C_{1-4} alkyl is optionally substituted with one or more substituents independently selected from OH and F. It is more preferred that E is phenyl, pyridine, benzimidazole, indazole, quinoline, isoquinoline, pyridine-(N)-oxide, benzothiophene, indole, azaindole, benzofuran, benzisoxazole, benzoxazole, benzothiazole.

It s also preferred that E is selected from the group consisting of



wherein

T and V are independently =CH-, =CR^{71}-, =N- or =N(O)-;

U is -NH-, -NR^{72}-, -O-, or -S-, wherein

R^{67}, R^{68}, R^{69}, R^{70}, R^{71} are independently selected from the group consisting of

hydrogen;

C_{3-6} cycloalkyl;

E^6;

E^7;

halogen;

$-N(R^{73}R^{74})$;

-OH; and

$-COOR^{75}$ or $-C(O)NR^{76}R^{77}$;

and wherein R^{72}, R^{73}, R^{74}, R^{75}, R^{76}, R^{77} are independently

hydrogen;

C_{1-4} alkyl; or

$-C(O)-C_{1-4}$ alkyl;

E^6 is selected from the group consisting of C_{1-6} alkyl; $-O-C_{1-6}$ alkyl; and $-N(R^{78})-C_{1-6}$ alkyl, wherein the C_{1-6} alkyl group is optionally substituted with one or more of

halogen;

$-N(R^{79}R^{80})$;

phenyl, optionally substituted with chloro;

heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, $-S(O)-$, $-S(O_2)-$, -N=, $-N(O)=$ and $-N(R^{81})-$, optionally substituted with chloro;

and/or E^6 is optionally interrupted by one or more of oxygen;

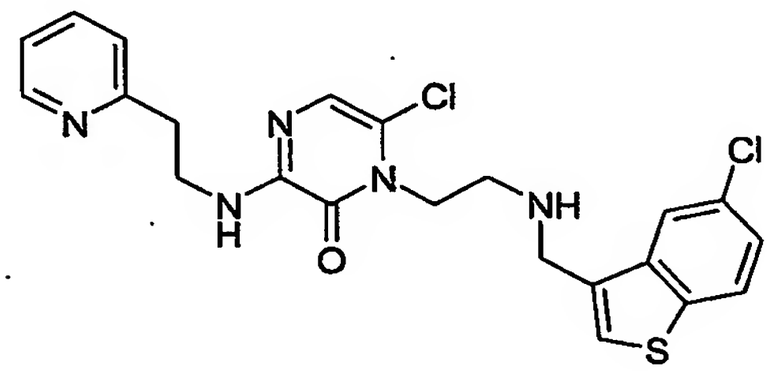
and wherein R^{78}, R^{79}, R^{80}, R^{81} are independently hydrogen, C_{1-4}alkyl;

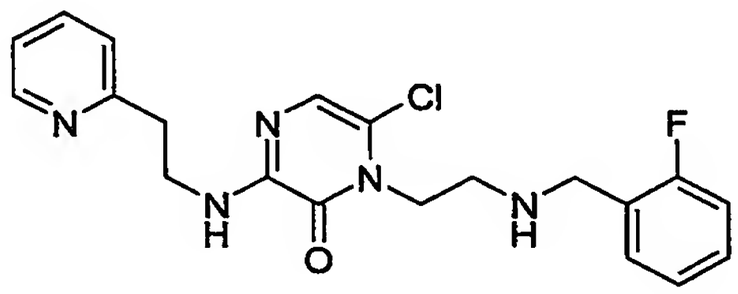
E^7 is selected from the group consisting of E^8; $-O-E^8$; $-N(R^{82})-E^8$; and $-C(O)-E^8$, wherein E^8 is phenyl or heterocycle containing up to 4 heteroatoms, which are the same or different and selected from the group consisting of -O-, -S-, $-S(O)-$, $-S(O_2)-$, -N=, $-N(O)=$ and $-N(R^{83})-$; and wherein E^8 is optionally substituted with chloro or $-N(R^{84}R^{85})$; and wherein R^{82}, R^{83}, R^{84}, R^{85} are independently hydrogen or C_{1-4} alkyl.

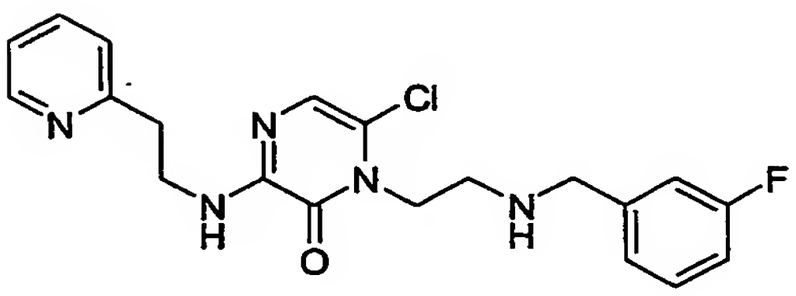
Preferably, R^{67}, R^{68}, R^{69}, R^{70}, R^{71} are independently hydrogen, fluoro, chloro, cyano, phenyl, chlorophenyl, methyl, methoxy, amino, monomethyl amino, dimethyl amino, pyrrolyl, diazolyl, triazolyl, and tetrazolyl.

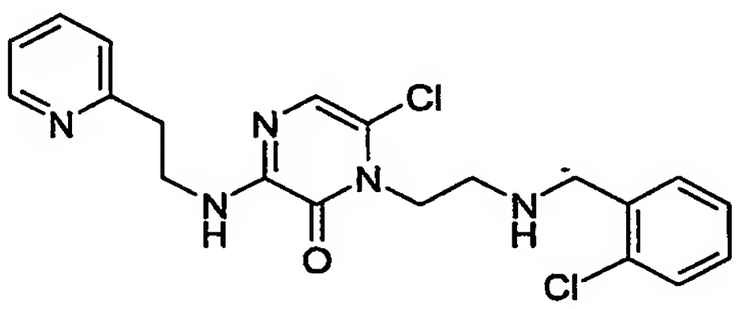
Compounds of the formula (I) in which some or all of the above-mentioned groups have the preferred or more preferred meanings are also an object of the present invention.

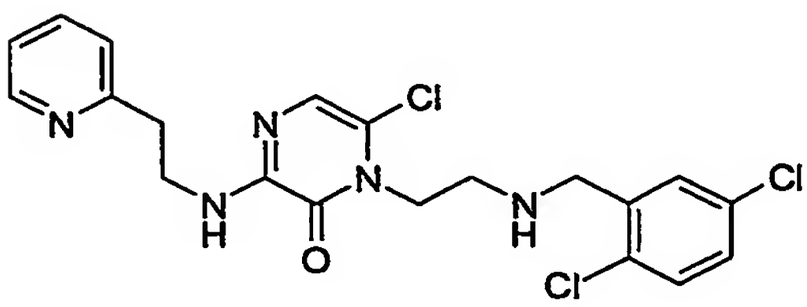
Preferred embodiments of the compounds according to present invention are shown below:

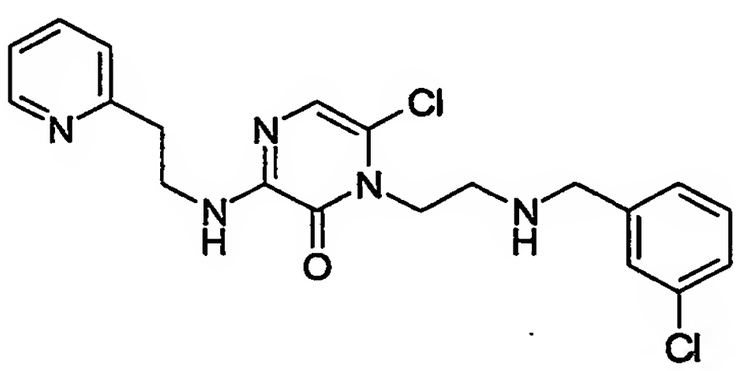


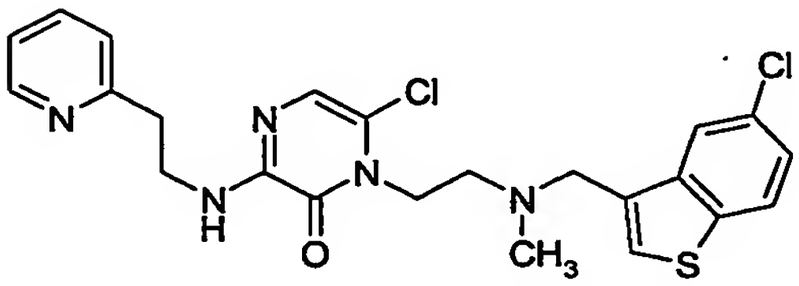


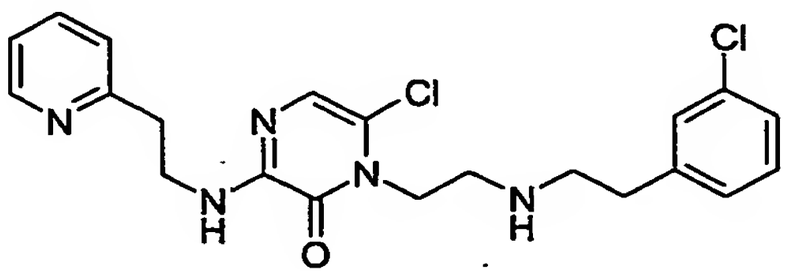


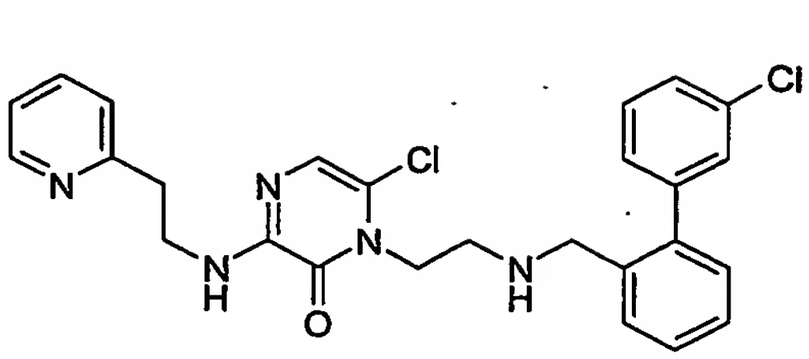


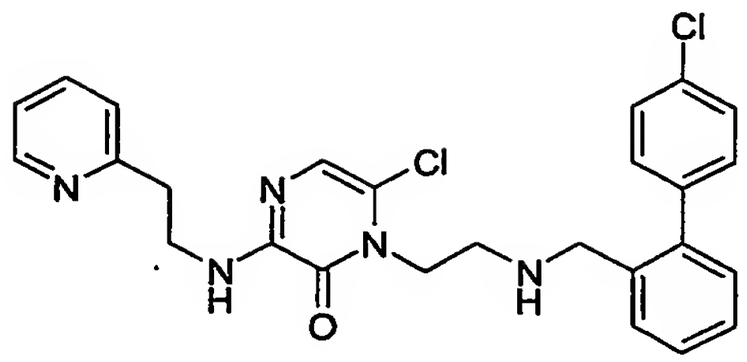


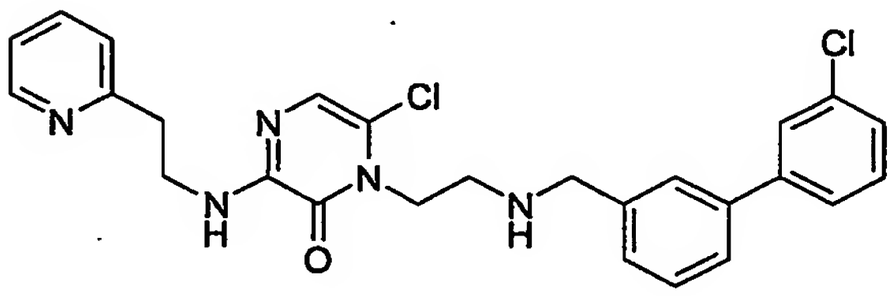


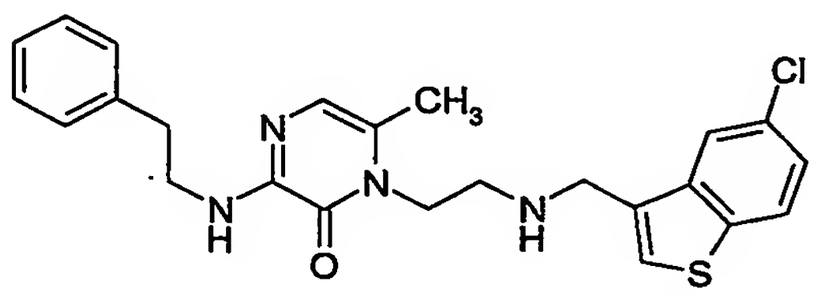


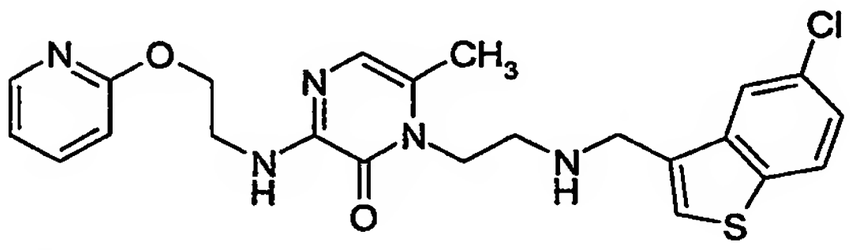


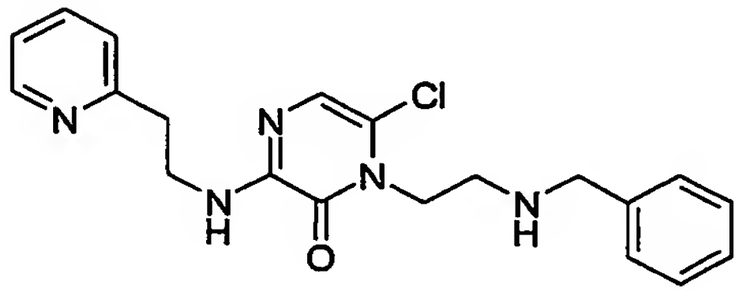


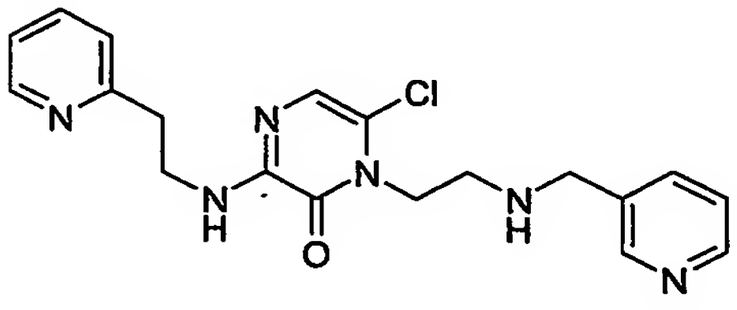


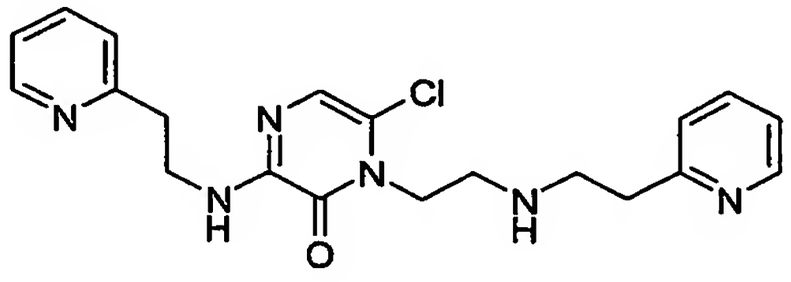


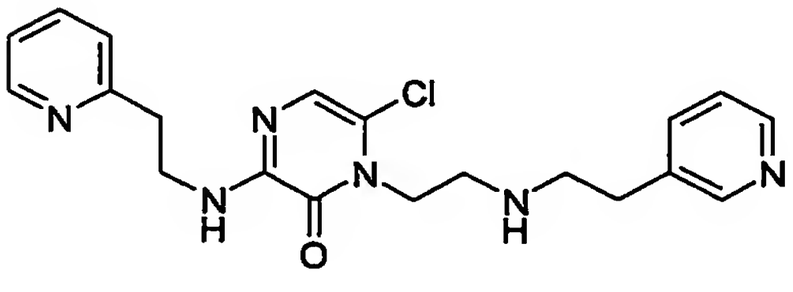


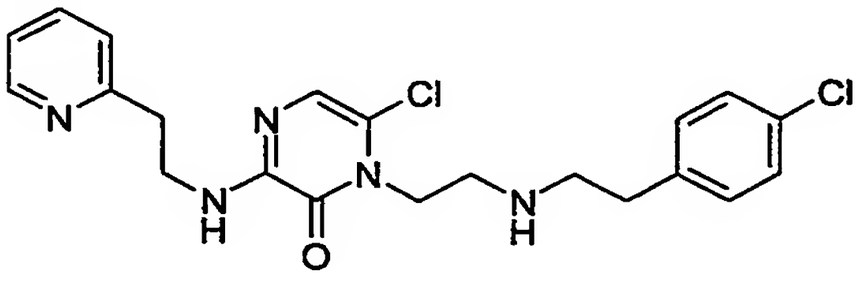


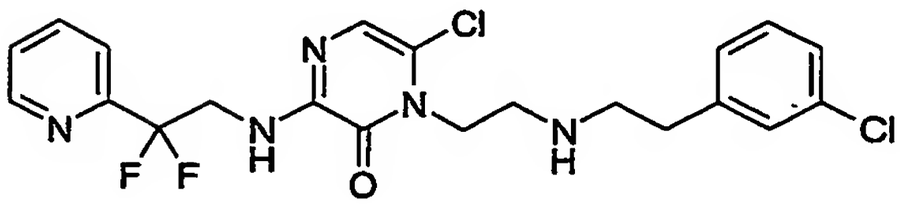


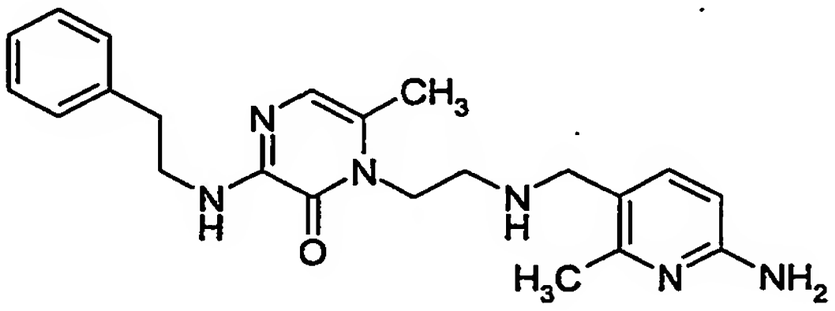


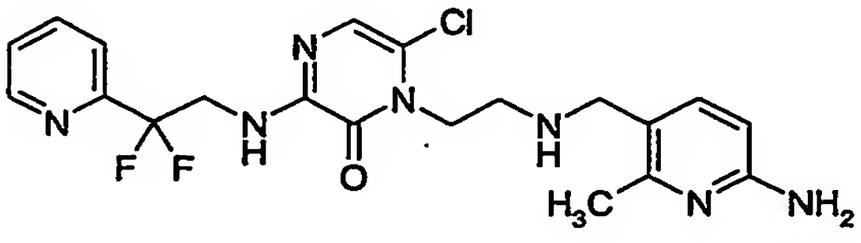


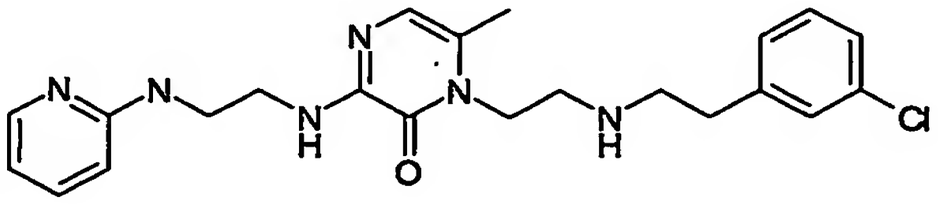


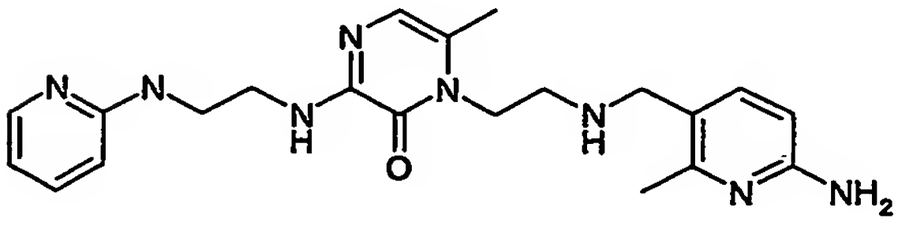


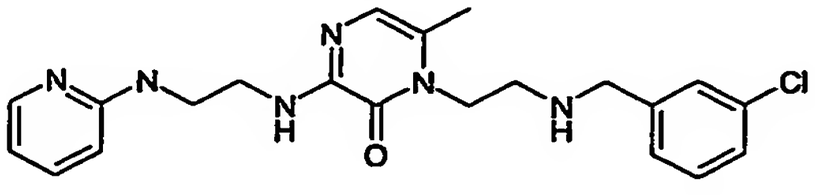


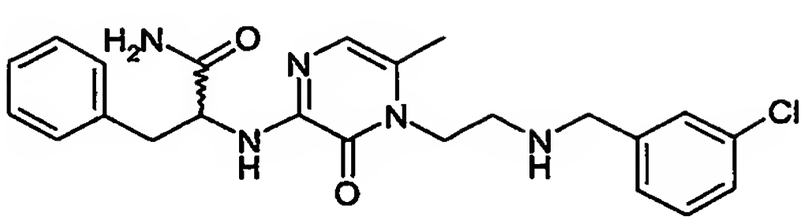


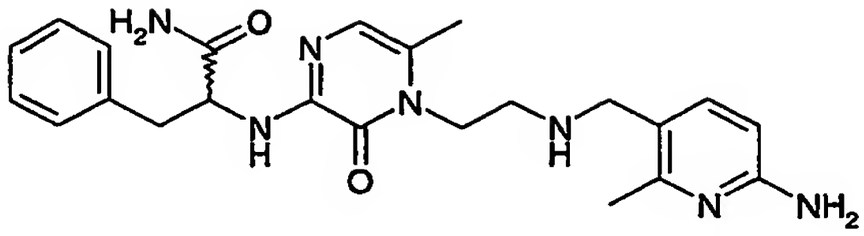


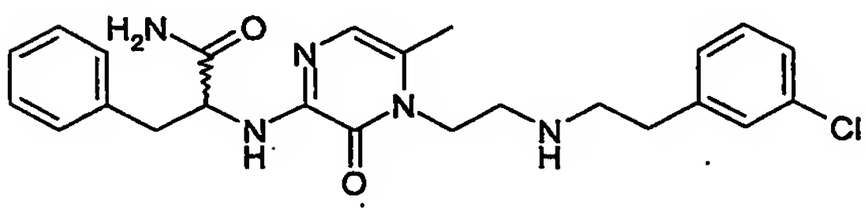


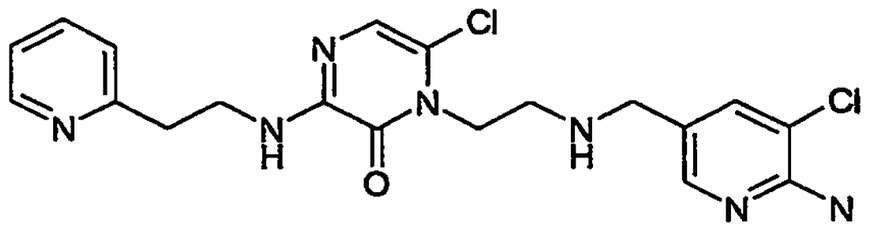


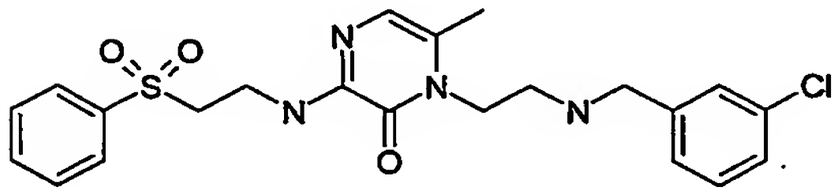


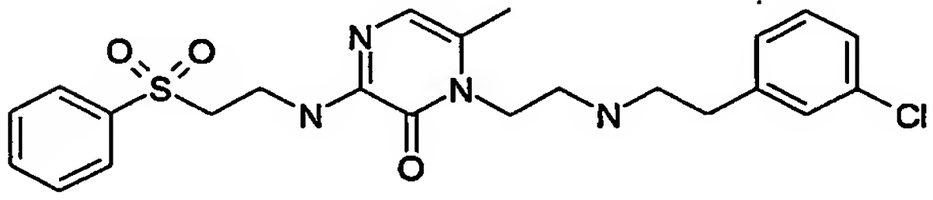


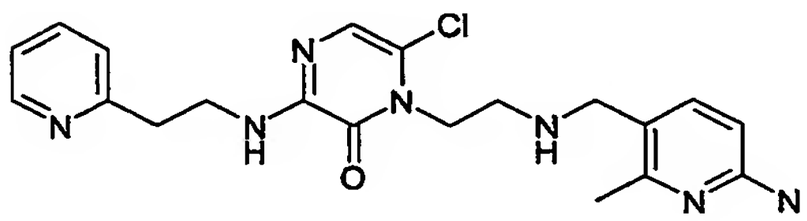


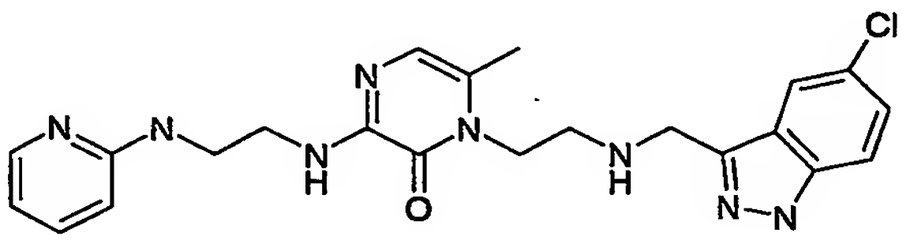


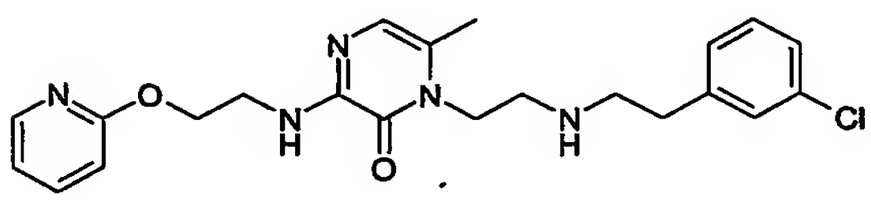


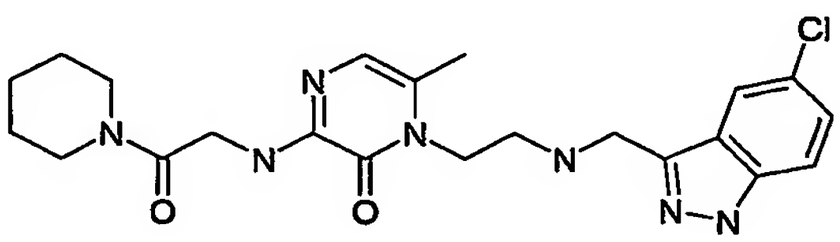


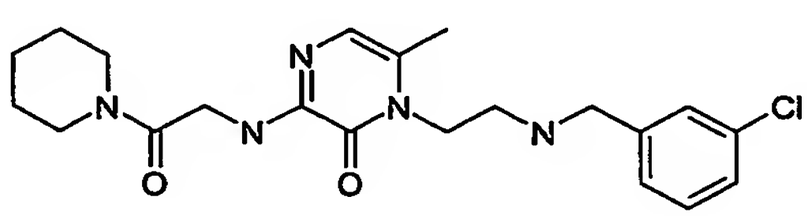


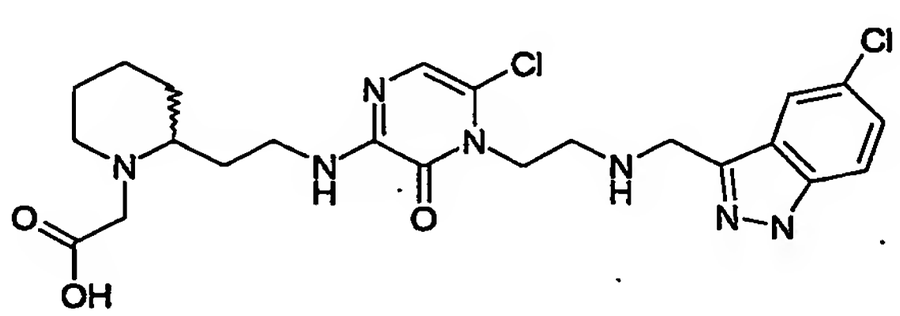


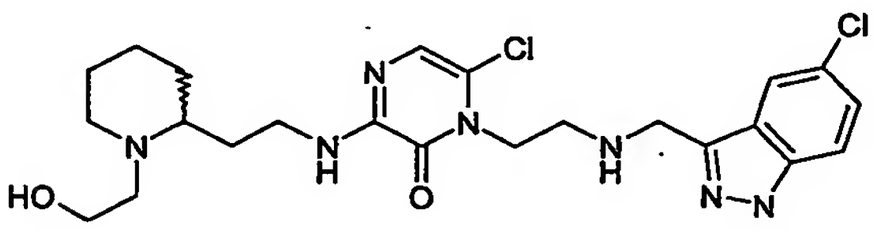


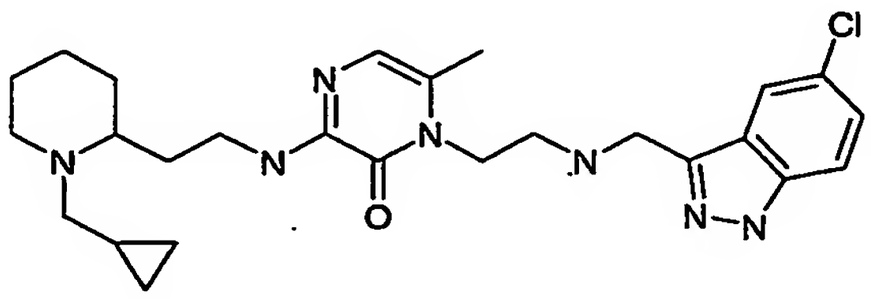


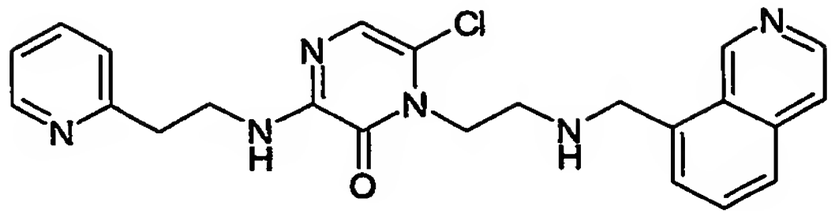


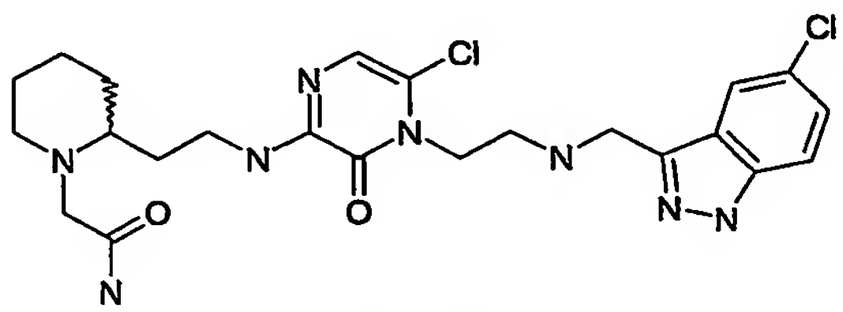


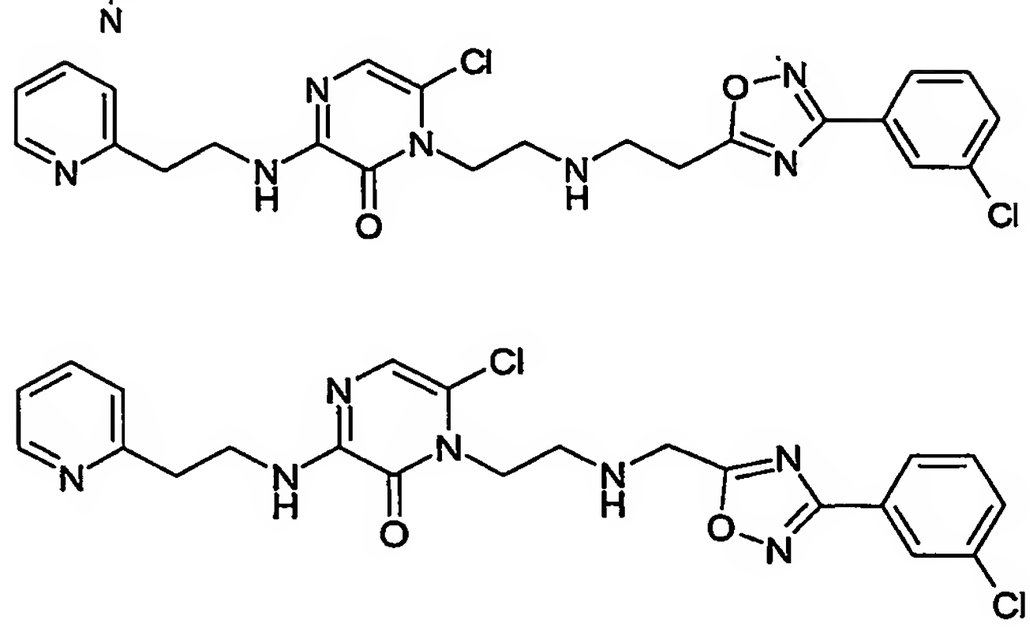


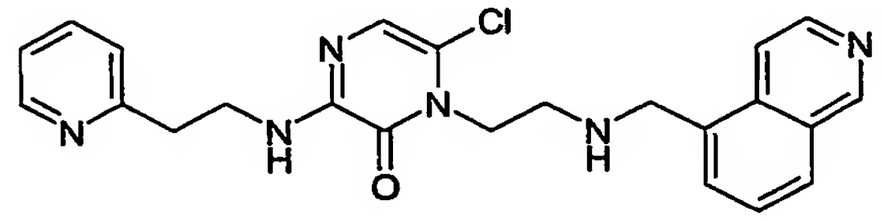


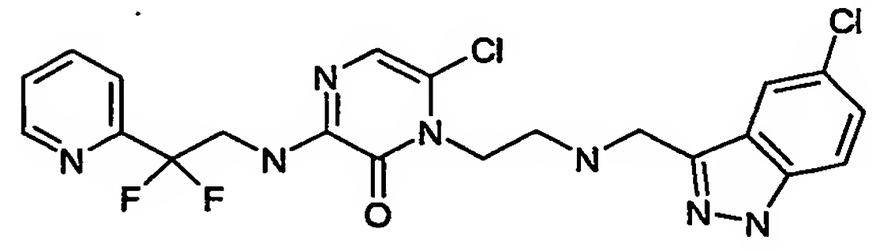


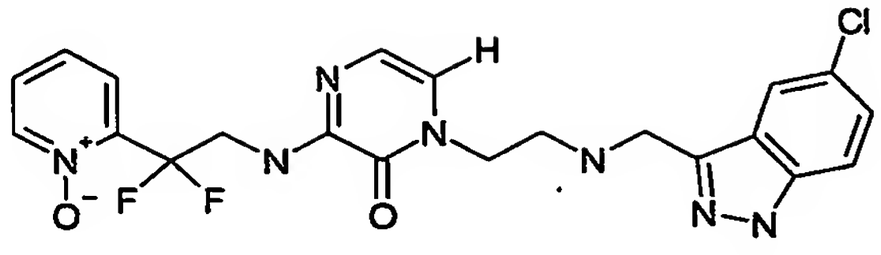


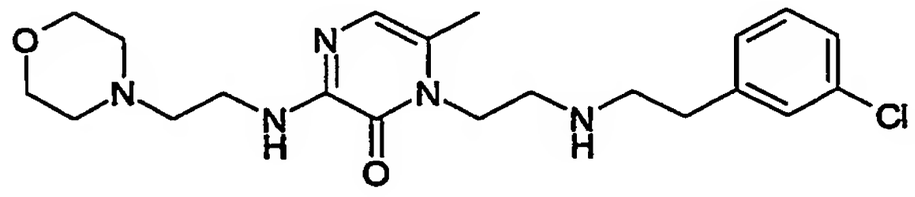


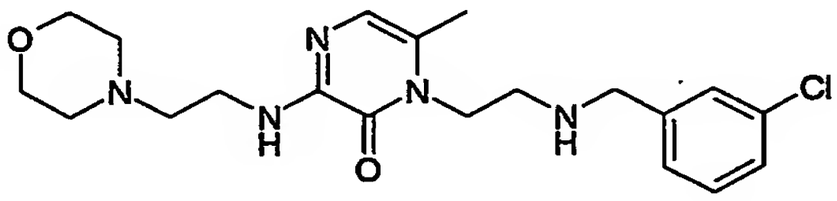


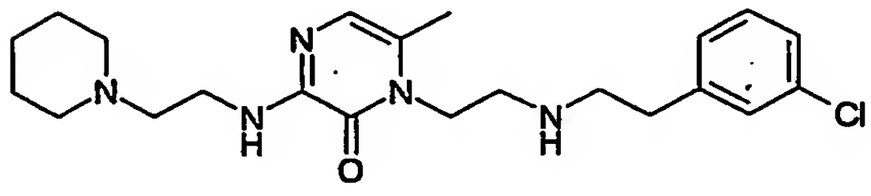


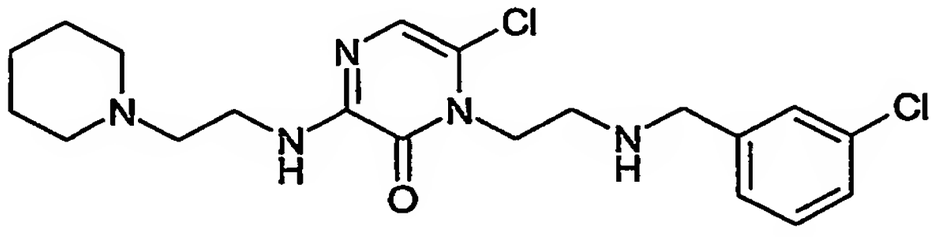


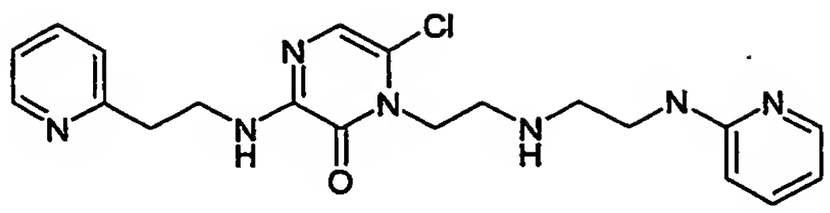


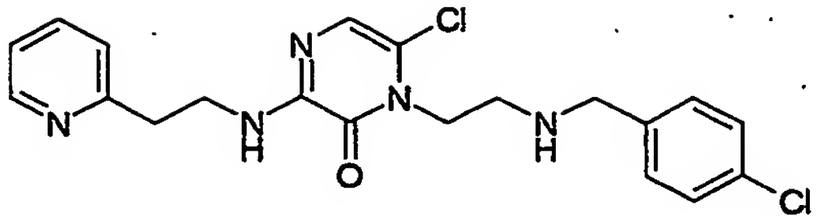


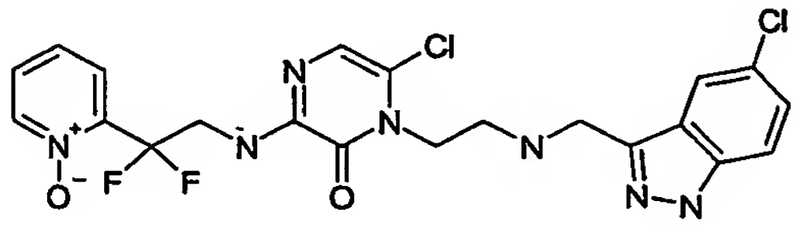


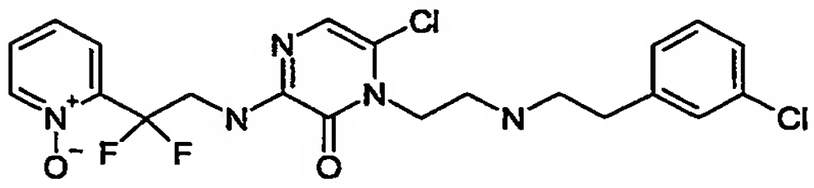


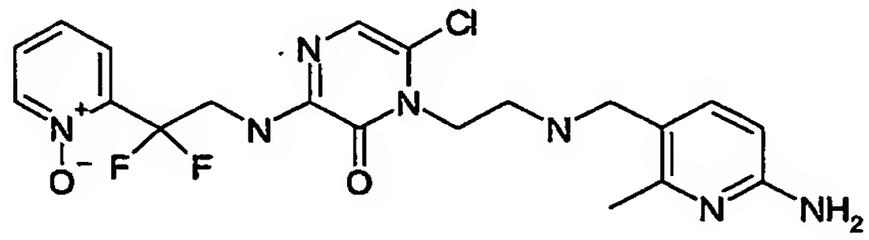


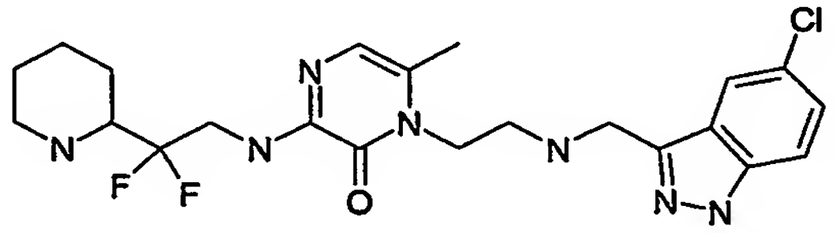


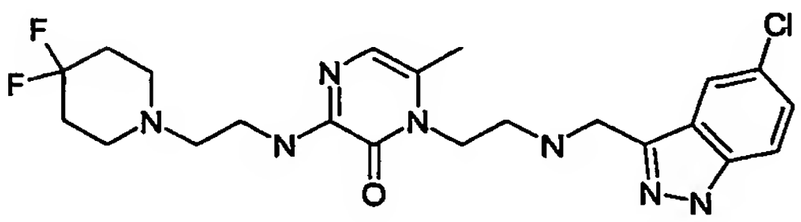


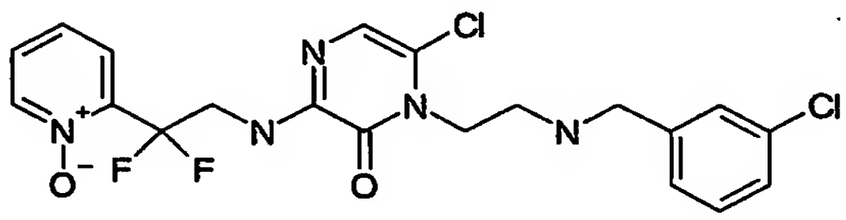


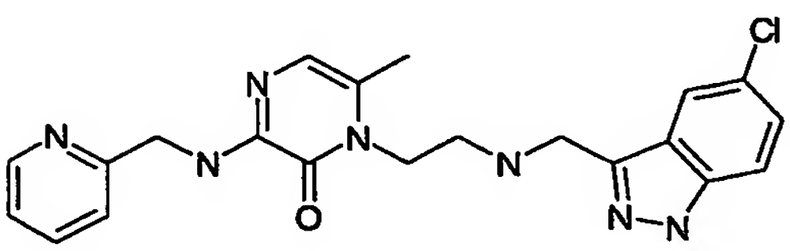


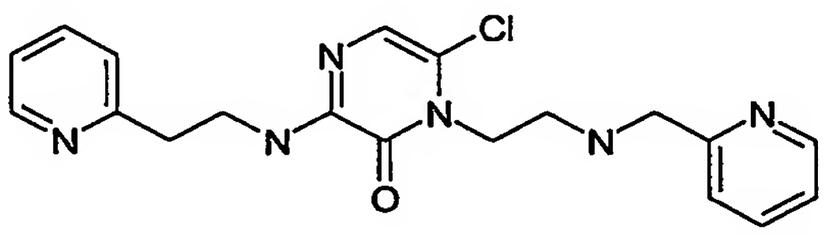


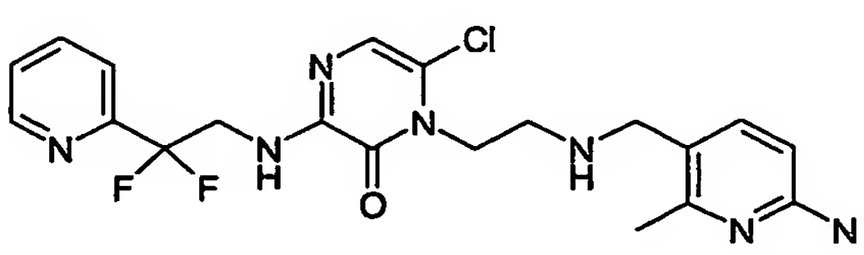


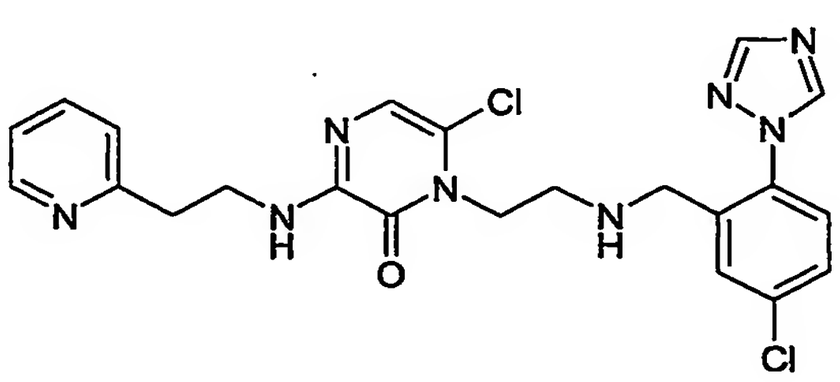


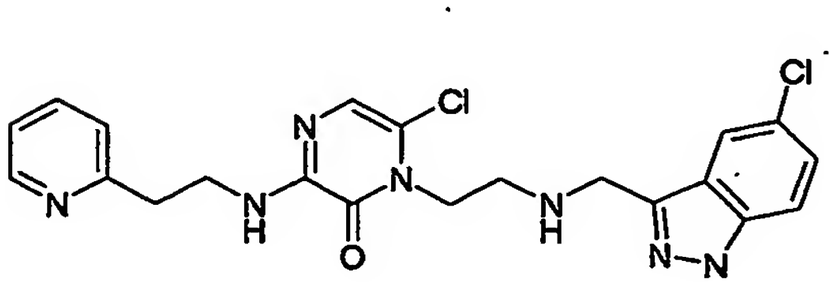


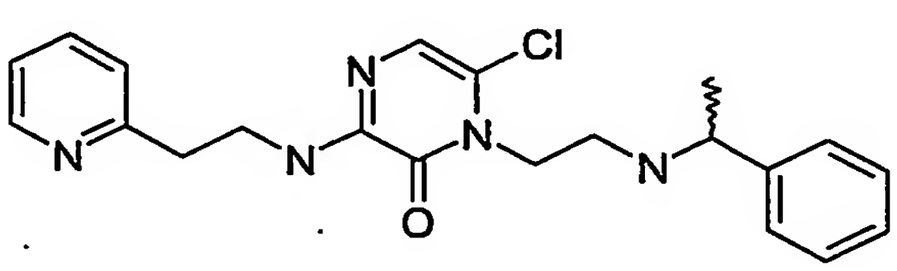


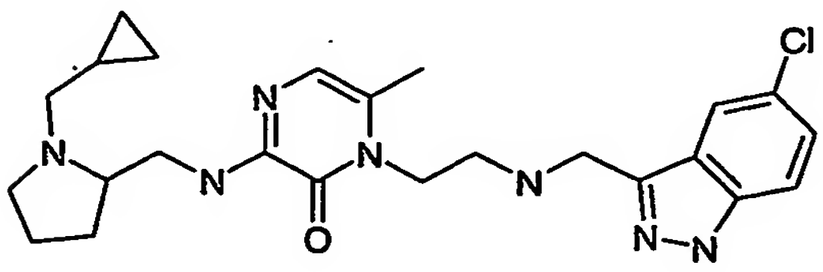


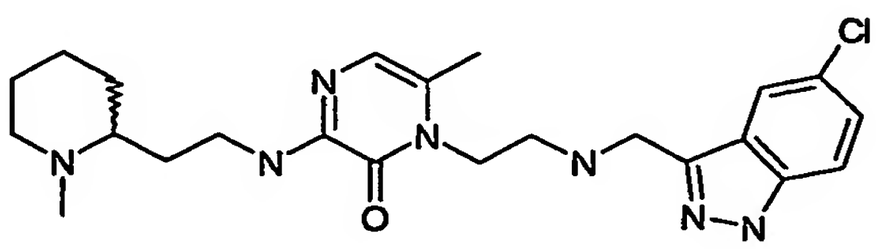


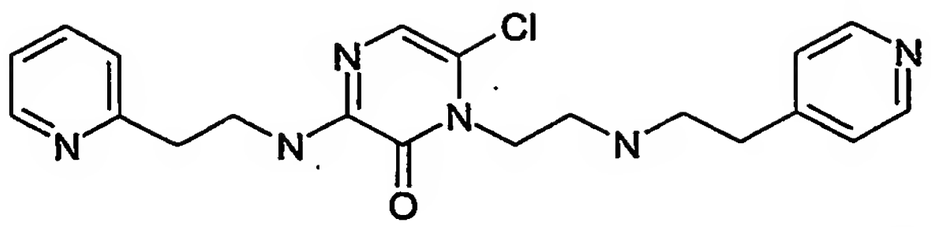


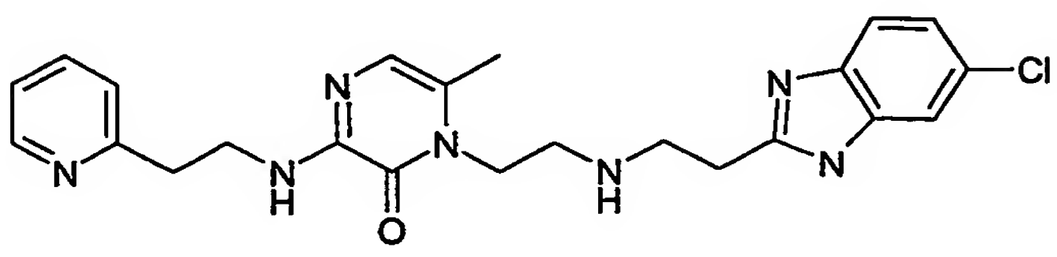


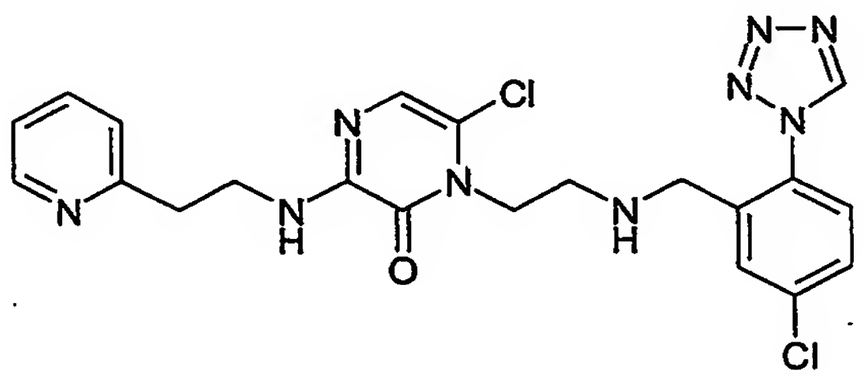


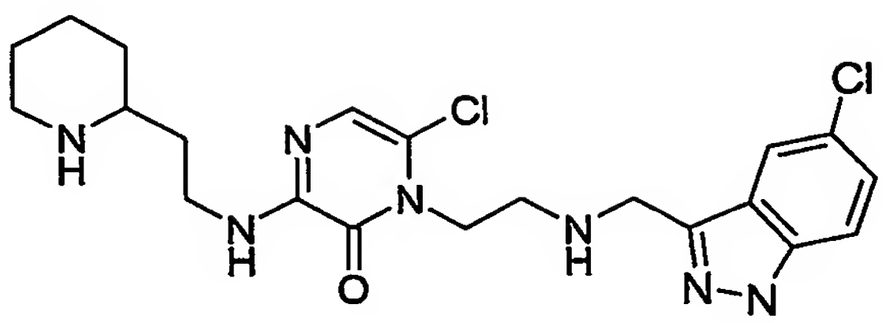


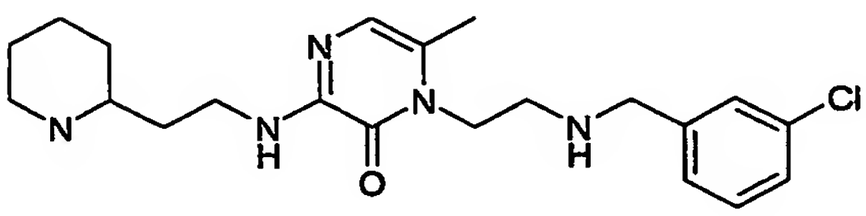


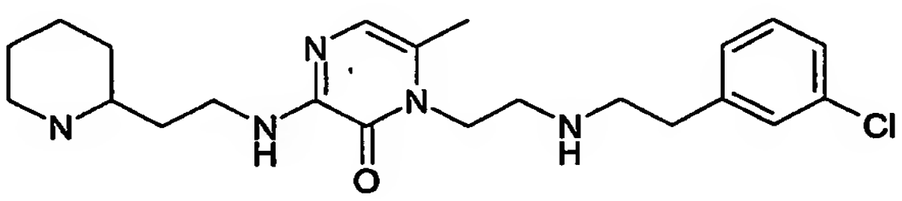


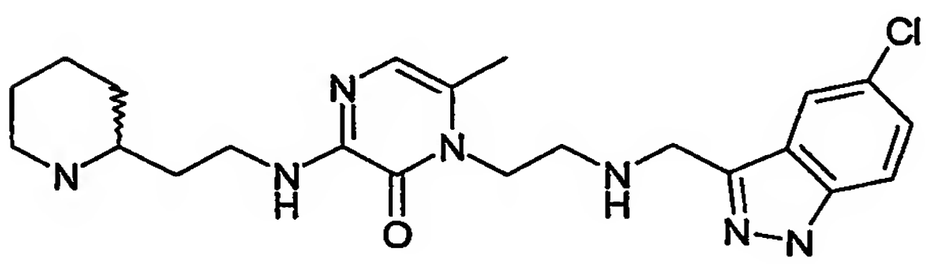


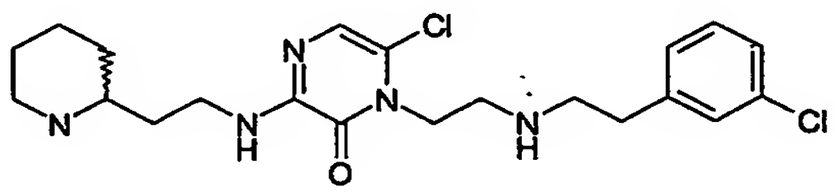


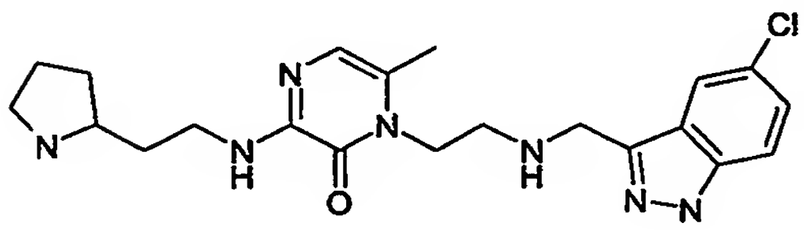


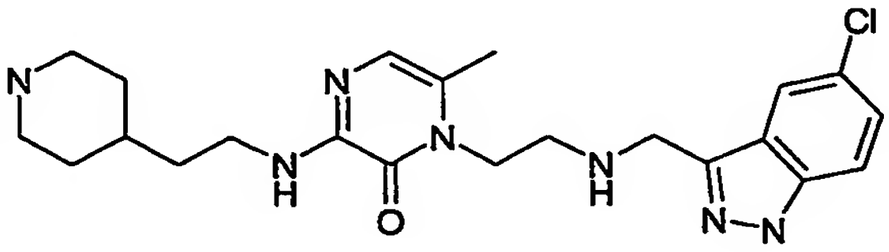


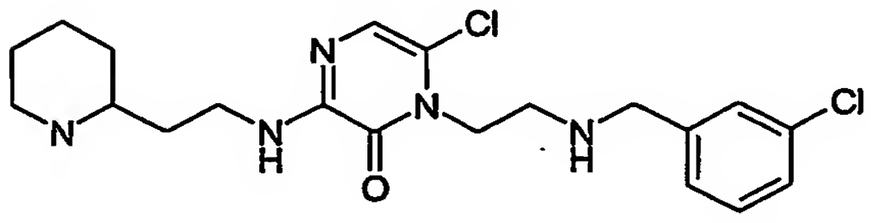


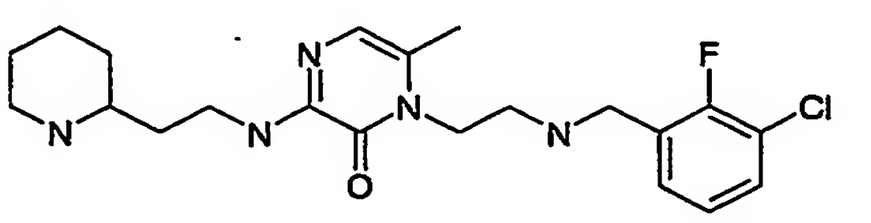












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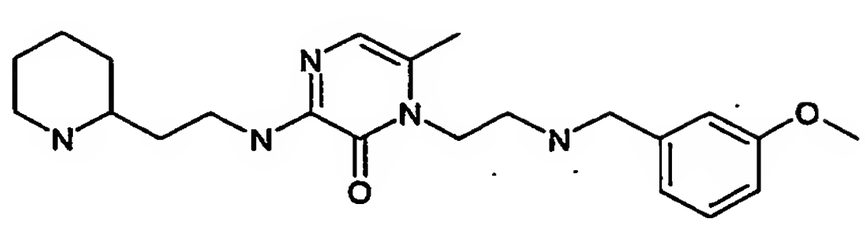
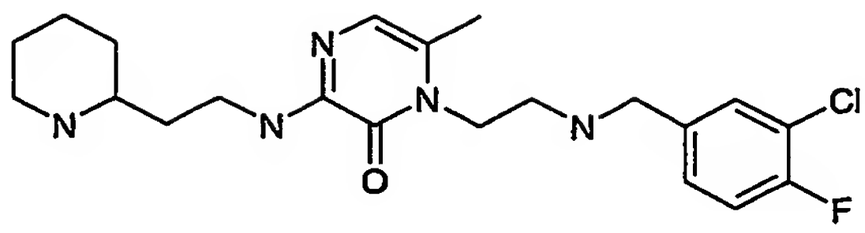
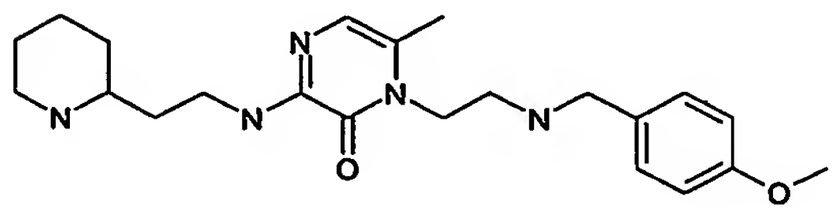
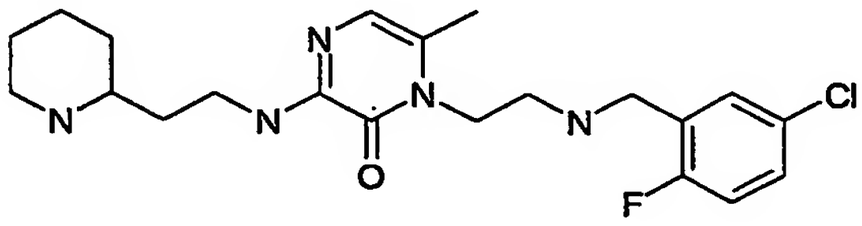
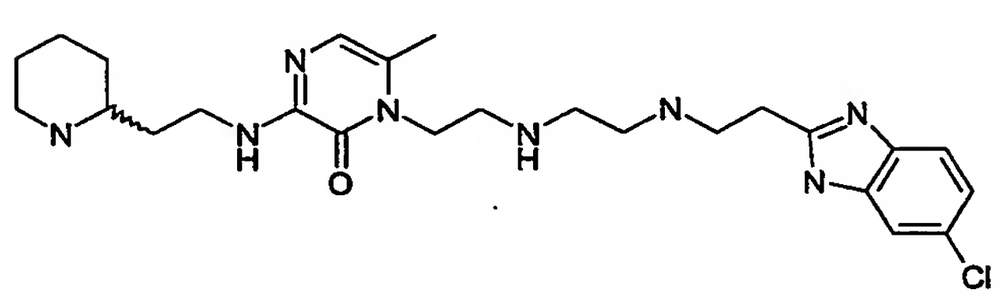
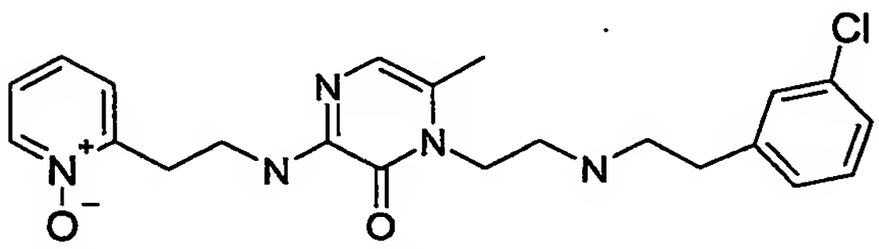


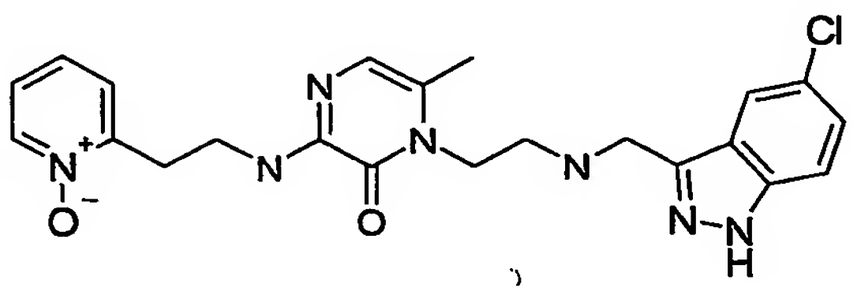


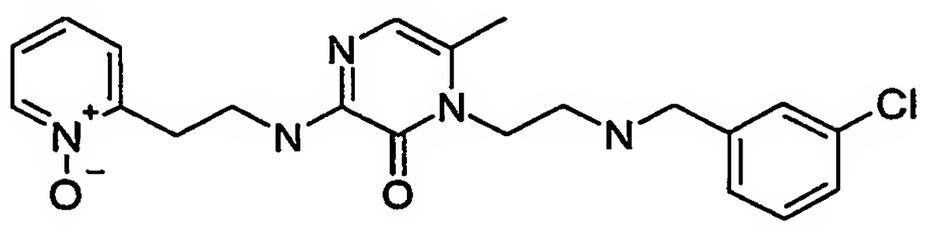












Furthermore, the present invention provides prodrugs of the compounds of the invention as described above.

"Prodrug" means a derivative that is converted into a compound according to the present invention by a reaction with an enzyme, gastric acid or the like under a physiological condition in the living body, e.g. by oxidation, reduction, hydrolysis or the like, each of which is carried out enzymatically. Examples of the prodrug are compounds, wherein the amino group in a compound of the present invention is acylated, alkylated or phosphorylated to form, e.g., eicosanoylamino, alanylamino, pivaloyloxymethylamino or wherein the hydroxyl group is acylated, alkylated, phosphorylated or converted into the borate, e.g. acetyloxy, palmitoyloxy, pivaloyloxy, succinyloxy, fumaryloxy, alanyloxy or wherein the carboxyl group is esterified or amidated. These compounds can be produced from compounds of the present invention according to well-known methods.

Where tautomerism, like e.g. keto-enol tautomerism, of compounds of general formula (I) or their prodrugs may occur, the individual forms, like e.g. the keto and enol form, are claimed separately and together as mixtures. Same applies for stereoisomers, like e.g. enantiomers, cis/trans isomers, conformers and the like.

In case the compounds according to formula (I) contain one or more acidic or basic groups, the invention also comprises their corresponding pharmaceutically or toxicologically acceptable salts, in particular their pharmaceutically utilizable salts. Thus, the compounds of the formula (I) which contain acidic groups can be present on these groups and can be used according to the invention, for example, as alkali metal salts, alkaline earth metal salts or as ammonium salts. More precise examples of such salts include sodium salts, potassium salts, calcium salts, magnesium salts or salts with ammonia or organic amines such as, for example, ethylamine, ethanolamine, triethanolamine or amino acids. Compounds of the formula (I) which contain one or more basic groups, i.e. groups which can be protonated, can be present and can be used according to the invention in the form of their addition salts with inorganic or organic acids. Examples for suitable acids include hydrogen chloride, hydrogen bromide, phosphoric acid, sulfuric acid, nitric acid, methanesulfonic acid, p-toluenesulfonic acid, naphthalenedisulfonic acids, oxalic acid, acetic acid, tartaric acid, lactic acid, salicylic acid, benzoic acid, formic acid, propionic acid, pivalic acid, diethylacetic acid, malonic acid, succinic acid, pimelic acid, fumaric acid, maleic acid, malic acid, sulfaminic acid, phenylpropionic acid, gluconic acid, ascorbic acid, isonicotinic acid, citric acid, adipic acid, and other acids known to the person skilled in the art. If the compounds of the formula (I) simultaneously contain acidic and basic groups in the molecule, the invention also includes, in addition to the salt forms mentioned, inner salts or betaines (zwitterions). The respective salts according to the formula (I) can be obtained by customary methods which are known to the person skilled in the art like, for example by contacting these with an organic or inorganic acid or base in a solvent or dispersant, or by anion exchange or cation exchange with other salts. The present invention also includes all salts of the compounds of the formula (I) which, owing to low physiological compatibility, are not directly suitable for use in pharmaceuticals but which can be used, for example, as intermediates for chemical reactions or for the preparation of pharmaceutically acceptable salts.

The present invention provides compounds of general formula (I) or their prodrugs as anticoagulants or thrombin inhibitors. This includes compounds for inhibiting thrombus formation, and inhibiting embolus formation in a mammal, inhibiting loss of blood platelets, inhibiting formation of blood platelet aggregates, inhibiting formation of fibrin. These compounds may optionally include anticoagulants, antiplatelet agents, and thrombolytic agents. The compounds can be added to blood, blood products, or mammalian organs in order to effect the desired inhibitions.

Furthermore, the invention includes compounds of formula (I) or their prodrugs or pharmaceutically acceptable salts for use as a medicament and their use for the manufacture of a medicament for the treatment or prophylaxis of thromboembolism, thrombosis, artherosclerosis, unstable angina, refractory angina, myocardial infarction, transient ischemic attacks, atrial fibrillation, thrombotic stroke, embolic stroke, deep vein thrombosis, disseminated intravascular coagulation, ocular build up of fibrin, and reocclusion or restenosis of recanalized vessels.

The present invention also includes pharmaceutical compositions comprising a compound of formula (I) or their prodrugs or a mixture of compounds or prodrugs or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable carrier. Optionally, these pharmaceutical compositions may additionally comprise one or more known anticoagulants.

The therapeutic use and method of using anticoagulants or thrombin inhibitors like the compounds of formula (I) of the present invention or their prodrugs or their use for the manufacture of a medicament are well known in the art and are described in more detail in US 2003/01582218 A1 which is herewith incorporated by reference.

Accordingly, therapies based on anticoagulants are indicated for the prevention and treatment of a variety of thrombotic conditions, particularly coronary artery and cerebrovascular disease. Those experienced in this field are readily aware of the circumstances requiring anticoagulant therapy. The term "patient" used herein is taken to mean mammals such as primates, including humans, sheep, horses, cattle, pigs, rabbits, dogs, cats, rats, and mice.

Compounds of the present invention are useful for treating or preventing venous

thromboembolism (e. g. obstruction or occlusion of a vein by a detached thrombus; obstruction or occlusion of a lung artery by a detached thrombus), cardiogenic thromboembolism (e. g. obstruction or occlusion of the heart by a detached thrombus), arterial thrombosis (e. g. formation of a thrombus within an artery that may cause infarction of tissue supplied by the artery), atherosclerosis (e. g. arteriosclerosis characterized by irregularly distributed lipid deposits) in mammals, and for lowering the propensity of devices that come into contact with blood to clot blood.

Examples of venous thromboembolism which may be treated or prevented with compounds of the invention include obstruction of a vein, obstruction of a lung artery (pulmonary embolism), deep vein thrombosis, thrombosis associated with cancer and cancer chemotherapy, thrombosis inherited with thrombophilic diseases such as Protein C deficiency, Protein S deficiency, antithrombin III deficiency, and Factor V Leiden, and thrombosis resulting from acquired thrombophilic disorders such as systemic lupus erythematosus (inflammatory connective tissue disease). Also with regard to venous thromboembolism, compounds of the invention are useful for maintaining patency of indwelling catheters.

Examples of cardiogenic thromboembolism which may be treated or prevented with compounds of the invention include thromboembolic stroke (detached thrombus causing neurological affliction related to impaired cerebral blood supply), cardiogenic thromboembolism associated with atrial fibrillation (rapid, irregular twitching of upper heart chamber muscular fibrils), cardiogenic thromboembolism associated with prosthetic heart valves such as mechanical heart valves, and cardiogenic thromboembolism associated with heart disease.

Examples of arterial thrombosis include unstable angina (severe constrictive pain in chest of coronary origin), myocardial infarction (heart muscle cell death resulting from insufficient blood supply), ischemic heart disease (local anemia due to obstruction (such as by arterial narrowing) of blood supply), reocclusion during or after percutaneous transluminal coronary angioplasty, restenosis after percutaneous transluminal coronary angioplasty, occlusion of coronary artery bypass grafts, and occlusive cerebrovascular disease. Also with regard to arterial thrombosis, compounds of the present invention are useful for maintaining patency in arteriovenous cannulas.

Examples of atherosclerosis include arteriosclerosis.

Thrombin inhibition is useful not only in the anticoagulant therapy of individuals having thrombotic conditions, but is useful whenever inhibition of blood coagulation is required such as to prevent coagulation of stored whole blood and to prevent coagulation in other biological samples for testing or storage. Thus, the thrombin inhibitors can be added to or contacted with any medium containing or suspected of containing thrombin and in which it is desired that blood coagulation be inhibited, e. g., when contacting the mammal's blood with material selected from the group consisting of vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems.

Examples of devices that come into contact with blood include vascular grafts, stents, orthopedic prosthesis, cardiac prosthesis, and extracorporeal circulation systems The thrombin inhibitors of the invention can be administered in such oral forms as tablets, capsules (each of which includes sustained release or timed release formulations), pills, powders, granules, elixers, tinctures, suspensions, syrups, and emulsions. Likewise, they may be administered in intravenous (bolus or infusion), intraperitoneal, subcutaneous, or intramuscular form, all using forms well known to those of ordinary skill in the pharmaceutical arts. An effective but nontoxic amount of the compound desired can be employed as an anti-aggregation agent.

For treating ocular build up of fibrin, the compounds may be administered intraocularly or topically as well as orally or parenterally.

The compounds of the present invention can be administered in the form of a depot injection or implant preparation which may be formulated in such a manner as to permit a sustained release of the active ingredient. The active ingredient can be compressed into pellets or small cylinders and implanted subcutaneously or intramuscularly as depot injections or implants. Implants may employ inert materials such as biodegradable polymers or synthetic silicones, for example, Silastic, silicone rubber or other polymers manufactured by the Dow-Corning Corporation.

The compounds of the present invention can also be administered in the form of

liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles and multilamellar vesicles. Liposomes can be formed from a variety of phospholipids, such as cholesterol, stearylamine or phosphatidylcholines.

The compounds of the present invention may also be delivered by the use of monoclonal antibodies as individual carriers to which the compound molecules are coupled. The compounds of the present invention may also be coupled with soluble polymers as targetable drug carriers. Such polymers can include polyvinlypyrrolidone, pyran copolymer, polyhydroxy-propyl-methacrylamide-phenol, polyhydroxyethylaspartamide-phenol, or polyethyleneoxide-polylysine substituted with palmitoyl residues. Furthermore, the thrombin inhibitors may be coupled to a class of biodegradable polymers useful in achieving controlled release of a drug, for example, polylactic acid, polyglycolic acid, copolymers of polylactic and polyglycolic acid, polyepsilon caprolactone, polyhydroxy butyric acid, polyorthoesters, polyacetals, polydihydropyrans, polycyanoacrylates and cross linked or amphipathic block copolymers of hydrogels.

The dosage regimen utilizing the thrombin inhibitors is selected in accordance with a variety of factors including type, species, age, weight, sex and medical condition of the patient; the severity of the condition to be treated; the route of administration; the renal and hepatic function of the patient; and the particular compound or salt thereof employed. An ordinarily skilled physician or veterinarian can readily determine and prescribe the effective amount of the drug required to prevent, counter, or arrest the progress of the condition.

Oral dosages of the compounds of the present invention, when used for the indicated effects, will range between about 0.01 mg per kg of body weight per day (mg/kg/day) to about 30 mg/kg/day, preferably 0.025-7.5 mg/kg/day, more preferably 0.1-2.5 mg/kg/day, and most preferably 0.1-0.5 mg/kg/day (unless specificed otherwise, amounts of active ingredients are on free base basis). For example, an 80 kg patient would receive between about 0.8 mg/day and 2.4 g/day, preferably 2-600 mg/day, more preferably 8-200 mg/day, and most preferably 8-40 mg/kg/day. A suitably prepared medicament for once a day administration would thus contain between 0.8 mg and 2.4 g, preferably between 2 mg and 600 mg, more preferably between 8 mg and 200 mg, and most preferably 8 mg and 40 mg, e. g., 8 mg, 10 mg, 20 mg and 40 mg. Advantageously, the compounds of the present invention may be administered in

divided doses of two, three, or four times daily. For administration twice a day, a suitably prepared medicament would contain between 0.4 mg and 4 g, preferably between 1 mg and 300 mg, more preferably between 4 mg and 100 mg, and most preferably 4 mg and 20 mg, e. g., 4 mg, 5 mg, 10 mg and 20 mg.

Intravenously, the patient would receive the active ingredient in quantities sufficient to deliver between 0.025-7.5 mg/kg/day, preferably 0.1-2.5 mg/kg/day, and more preferably 0.1-0.5 mg/kg/day. Such quantities may be administered in a number of suitable ways, e. g. large volumes of low concentrations of active ingredient during one extended period of time or several times a day, low volumes of high concentrations of active ingredient during a short period of time, e. g. once a day. Typically, a conventional intravenous formulation may be prepared which contains a concentration of active ingredient of between about 0.01-1.0 mg/ml, e. g. 0.1 mg/ml, 0.3 mg/ml, and 0.6 mg/ml, and administered in amounts per day of between 0.01 ml/kg patient weight and 10.0 ml/kg patient weight, e. g. 0.1 ml/kg, 0.2 ml/kg, 0.5 ml/kg. In one example, an 80 kg patient, receiving 8 ml twice a day of an intravenous formulation having a concentration of active ingredient of 0.5 mg/ml, receives 8 mg of active ingredient per day. Glucuronic acid, L-lactic acid, acetic acid, citric acid or any pharmaceutically acceptable acid/conjugate base with reasonable buffering capacity in the pH range acceptable for intravenous administration may be used as buffers. Consideration should be given to the solubility of the drug in choosing an appropriate buffer and pH of a formulation, depending on solubility of the drug to be administered, is readily made by a person having ordinary skill in the art.

The compounds of the present invention can also be administered in intranasal form via topical use of suitable intranasal vehicles, or via transdermal routes, using those forms of transdermal skin patches well known to those of ordinary skill in that art. To be administered in the form of a transdermal delivery system, the dosage administration will, or course, be continuous rather than intermittent throughout the dosage regime.

The compounds of the present invention are typically administered as active ingredients in admixture with suitable pharmaceutical diluents, excipients or carriers (collectively referred to herein as "carrier" materials) suitably selected with respect to the intended form of administration, that is, oral tablets, capsules, elixers, syrups and the like, and consistent with convention pharmaceutical practices.

For instance, for oral administration in the form of a tablet or capsule, the active drug component can be combined with an oral, non-toxic, pharmaceutically acceptable, inert carrier such as lactose, starch, sucrose, glucose, methyl cellulose, magnesium stearate, dicalcium phosphate, calcium sulfate, mannitol, sorbitol and the like; for oral administration in liquid form, the oral drug components can be combined with any oral, non-toxic, pharmaceutically acceptable inert carrier such as ethanol, glycerol, water and the like. Moreover, when desired or necessary, suitable binders, lubricants, disintegrating agents and coloring agents can also be incorporated into the mixture. Suitable binders include starch, gelatin, natural sugars such as glucose or beta-lactose, corn-sweeteners, natural and synthetic gums such as acacia, tragacanth or sodium alginate, carboxymethylcellulose, polyethylene glycol, waxes and the like.

Lubricants used in these dosage forms include sodium oleate, sodium stearate, magnesium stearate, sodium benzoate, sodium acetate, sodium chloride and the like.

Disintegrators include, without limitation, starch methyl cellulose, agar, bentonite, xanthan gum and the like.

Typical uncoated tablet cores suitable for administration of thrombin inhibitors are comprised of, but not limited to, the following amounts of standard ingredients:

Excipient	General Range (%)	Preferred Range (%)	Most Preferred Range (%)
mannitol	10-90	25-75	30-60
microcrystalline	10-90	25-75	30-60
cellulose magnesium stearate	0.1-5.0	0.1-2.5	0.5-1.5

Mannitol, microcrystalline cellulose and magnesium stearate may be substituted with alternative pharmaceutically acceptable excipients.

The compounds of the present invention can also be co-administered with suitable antiplatelet agents, including, but not limited to, fibrinogen receptor antagonists (e. g. to

treat or prevent unstable angina or to prevent reocclusion after angioplasty and restenosis), anticoagulants such as aspirin, thrombolytic agents such as plasminogen activators or streptokinase to achieve synergistic effects in the treatment of various vascular pathologies, or lipid lowering agents including antihypercholesterolemics (e. g. HMG CoA reductase inhibitors such as lovastatin, HMG CoA synthase inhibitors, etc.) to treat or prevent atherosclerosis. For example, patients suffering from coronary artery disease, and patients subjected to angioplasty procedures, would benefit from coadministration of fibrinogen receptor antagonists and thrombin inhibitors of the present invention. Also, compounds of the present invention enhance the efficiency of tissue plasminogen activator-mediated thrombolytic reperfusion. Compounds of the present invention may be administered first following thrombus formation, and tissue plasminogen activator or other plasminogen activator is administered thereafter.

Typical doses of thrombin inhibitors of the present invention in combination with other suitable anti-platelet agents, anticoagulation agents, or thrombolytic agents may be the same as those doses of thrombin inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, or may be substantially less that those doses of thrombin inhibitors administered without coadministration of additional anti-platelet agents, anticoagulation agents, or thrombolytic agents, depending on a patient's therapeutic needs.

Compounds of formula (I) and their prodrugs as well as their intermediates and reagents can be prepared as set forth below. The various routes and examples for the synthesis of the compounds of the present invention are non-limiting. If they are neither commercially available nor subsequently described explicitly, they can be obtained by analogy to the strategies and examples described hereinafter, or by conventional synthetic procedures.

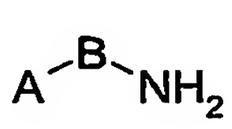
Some abbreviations that may appear in this application are as follows.

ABBREVIATIONS

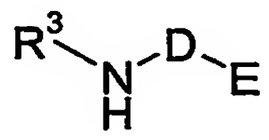
Designation	Coupling Reagent
Ac_2O	Acetic anhydride
bs	Broad singlet

Boc (or BOC)	*tert*-Butoxycarbonyl
Boc_2O	*tert*-Butyldicarbonate
DAST	Diethylaminosulfurtrifluoride
DCE	1,2-Dichloroethane
DCM	Dichloromethane
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
Et_2O	Diethylether
Et_3N	Triethylamine
EtOAc	Ethyl acetate
EtOH	Ethanol
HPLC	High pressure liquid chromatography
^iPrOH	Isopropyl alcohol
MCPBA	*meta*-Chloroperbenzoic acid
MsCl	Methanesulfonyl chloride
OGr	Organic leaving group based on oxygen
PG	Protecting group
PPh_3	Triphenylphosphine
rt	Retention time
Tf_2O	Trifluoromethanesulfonyl anhydride
TFA	Trifluoroacetic acid
TFAA	Trifluoroacetic acid anhydride
THF	Tetrahydrofuran
TLC	Thin layer chromatography

Readily available starting materials may be amines having the formula (II) or (III)



(II)

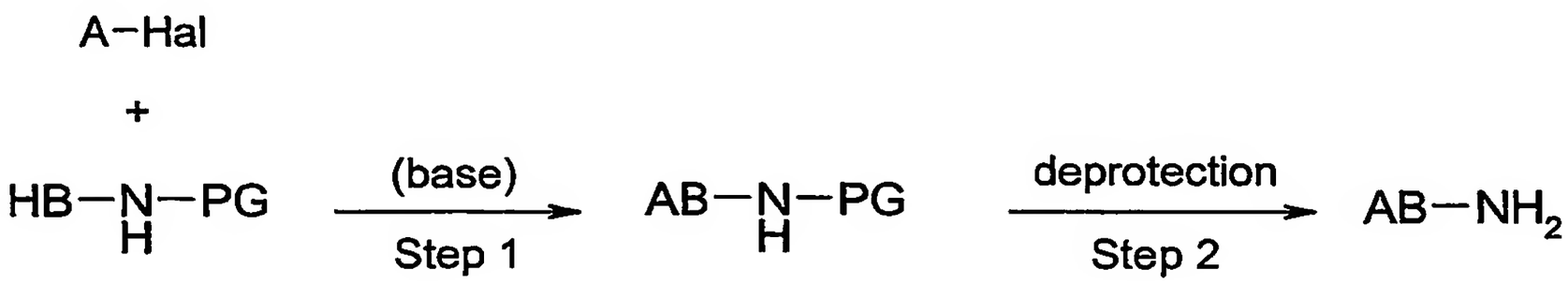


(III)

They may be purchased from commercially available sources such as Sigma-Aldrich, Fluka, ABCR or be synthesized by one skilled in the art. Common nucleophilic substitution reactions between compounds containing a suitable leaving group (e.g. halogenide, mesylate, tosylate) and nucleophiles (e.g. amines) may be employed. The conversion of diverse functional groups may allow the synthesis of various amines, e.g.

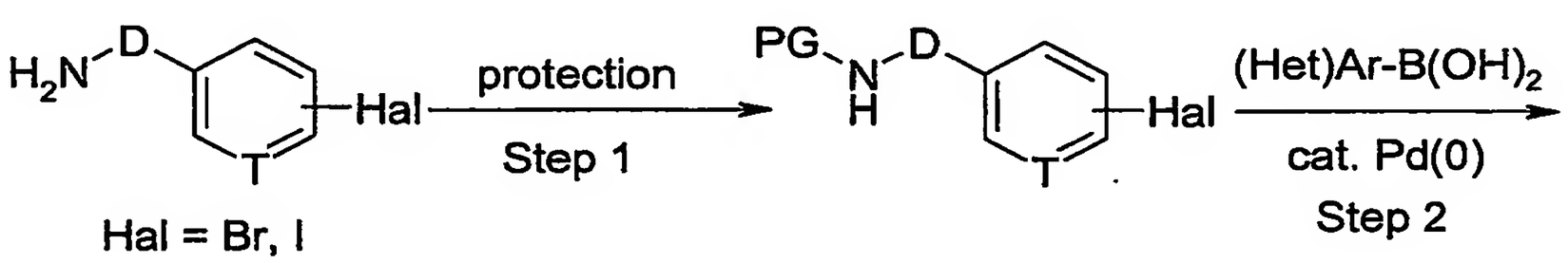
conversion of esters into acids, alcohols or amides intermediates; reduction of amides, nitriles or azides to amines; also novel carbon-nitrogen palladium-catalyzed coupling reactions with suitable functionalized starting materials. For the introduction of changes in the carbon chain attached to the nitrogen atom or for the synthesis of diverse (hetero)aryl derivatives, it may be possible to make use of diverse carbon-carbon coupling reactions, e.g. transition-metal catalyzed reactions, conventional techniques for ring closure, formylation of (hetero)aryls. Schemes A through D outline general procedures for the synthesis of some compounds described below. Unless otherwise indicated in the schemes, the variables have the same meaning as described above.

Scheme A

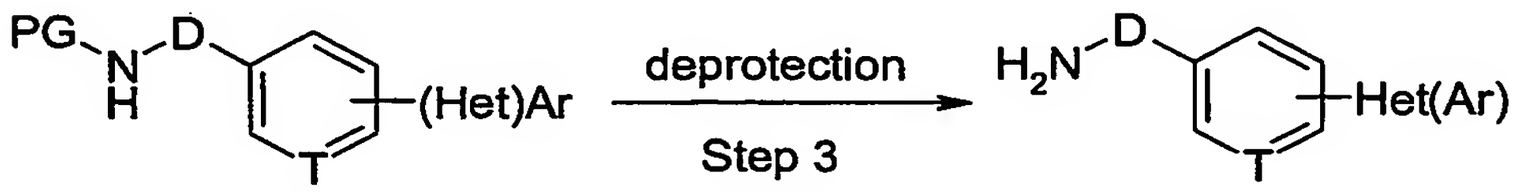


Hal = Cl, Br

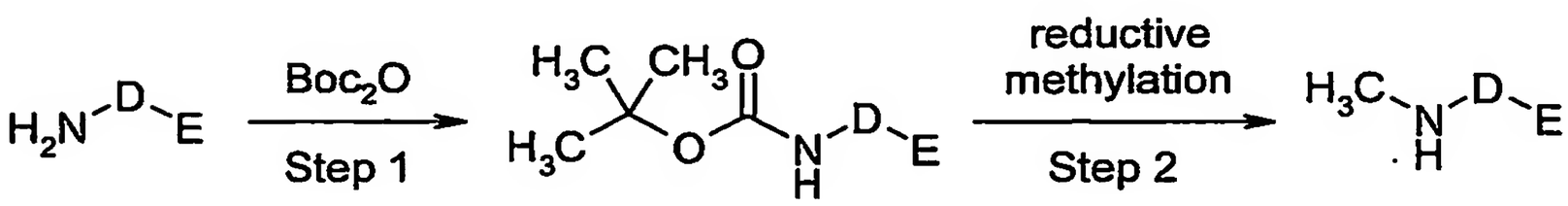
Scheme B



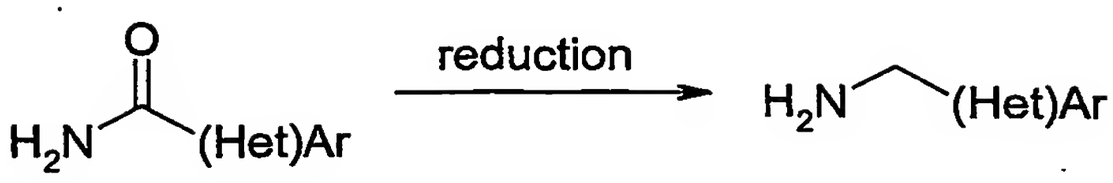
Hal = Br, I



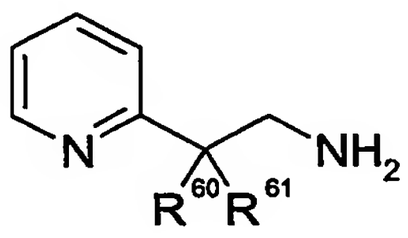
Scheme C



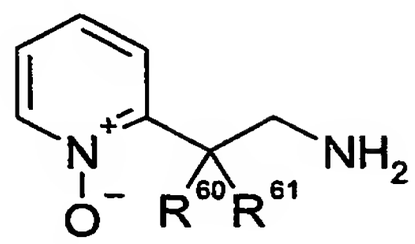
Scheme D



Amines having the formula (III) or (IV)



(III)

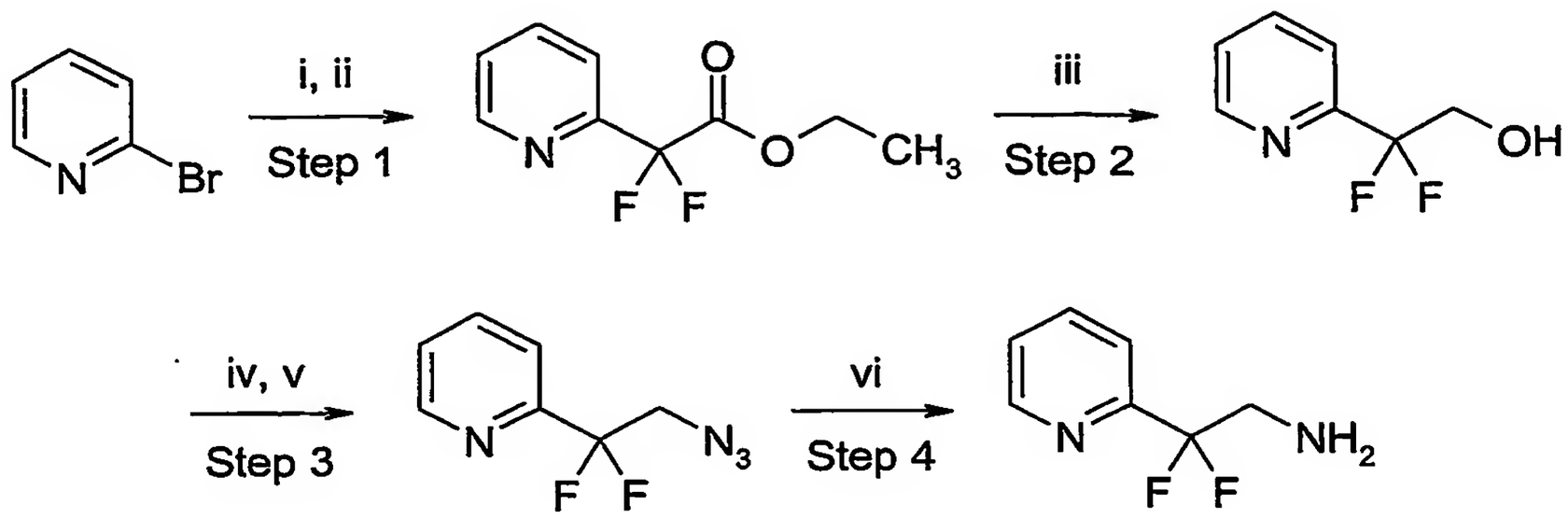


(IV)

R^{60}, R^{61} = H or F

may be conveniently prepared as described in WO 01/70229 or in *Bioorg. Med. Chem. Lett.*; 13; 2003; 1353-1357 and illustrated in Scheme E. 2-Bromopyridine reacts with diethyl oxalate and *n*-butyllithium to yield ethyl 2-pyridinoylformate, which can be treated with diethylaminosulfurtrifluoride (DAST) to give a *gem*-difluorinated ethyl acetate. This can alternatively be synthesised starting from ethyl 2-pyridyl acetate through electrophilic difluorination of its potassium enolate, according to the procedure described in *J. Med. Chem.*; 46; 2003; 461-473 or by copper coupling of 2-bromopyridine with bromo-difluoro-acetic acid ethyl ester according to the procedure described in *Tetrahedron Lett*; 2002: 9271-9274. The ethyl difluoro-2-pyridylacetate can then be reduced to the alcohol, converted into the triflate and the azide, and finally catalytically hydrogenated to yield 2,2-difluoro-2-(2-pyridyl)ethylamine.

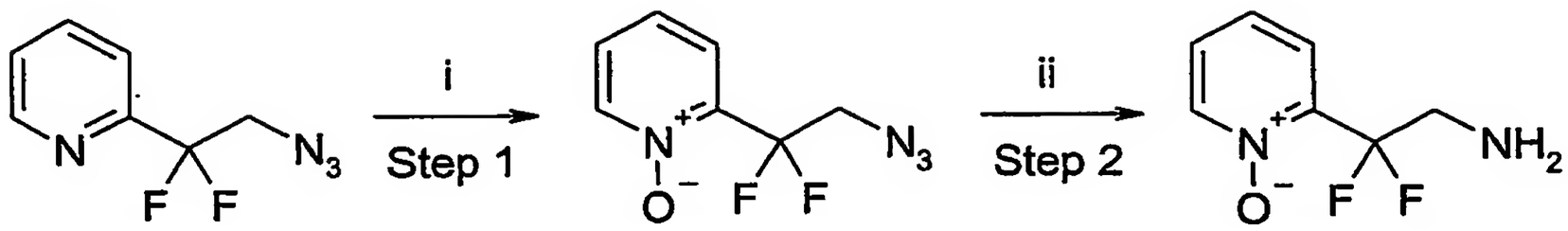
Scheme E



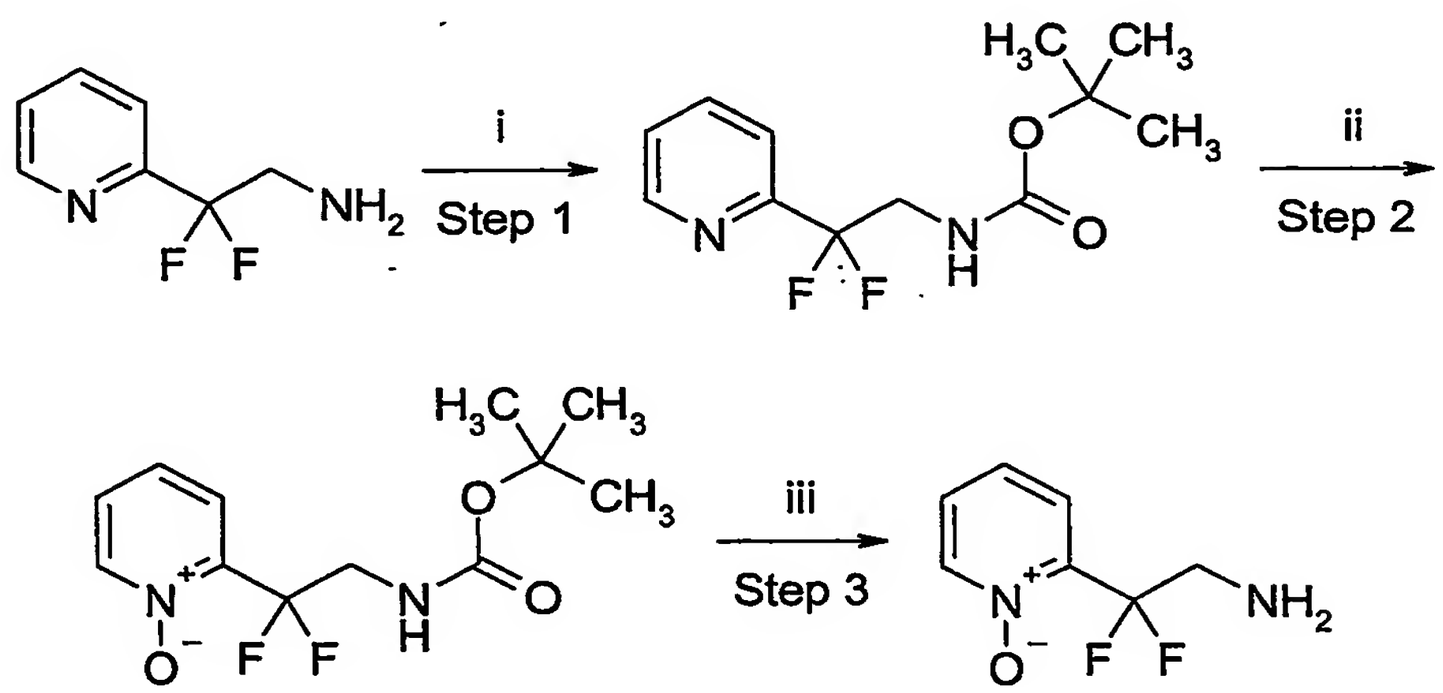
i. *n*BuLi, diethyl oxalate, Et_2O, 0 °C; ii. DAST, 55 °C; iii. $NaBH_4$, EtOH, 0 °C;
iv. Tf_2O, 2,6-di-*tert*-butyl-4-methylpyridine, -78°C, CH_2Cl_2; v. NaN_3, DMF, 60 °C;
vi. 1 atm H_2, 10% Pd/C, EtOAc

The synthesis of the 2,2-difluoro-2-(2-pyridyl-*N*-oxide)ethylamine may start with the azide, which may be prepared as outlined in Scheme E. For the oxidation of the pyridine it may be possible to follow one of the routes shown in Scheme F using *m*-chloroperbenzoic acid at elevated temperature in the presence of Kishi´s radical inhibitor as in *Bioorg. Med. Chem. Lett.*; 13; 2003; 1353-1357.

Scheme F

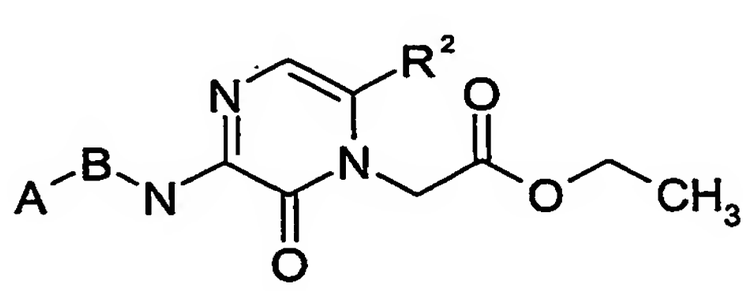


i. MCPBA, 55 °C, DCE; ii. PPh_3, THF; H_2O



i. Boc_2O, Et_3N, DCM, room temperature; ii. MCPBA, DCE, 60 °C;
iii. HCl / dioxan, room temperature

The 2*H*-pyrazin-1-yl-acetic acid ethyl esters with the formula (V)

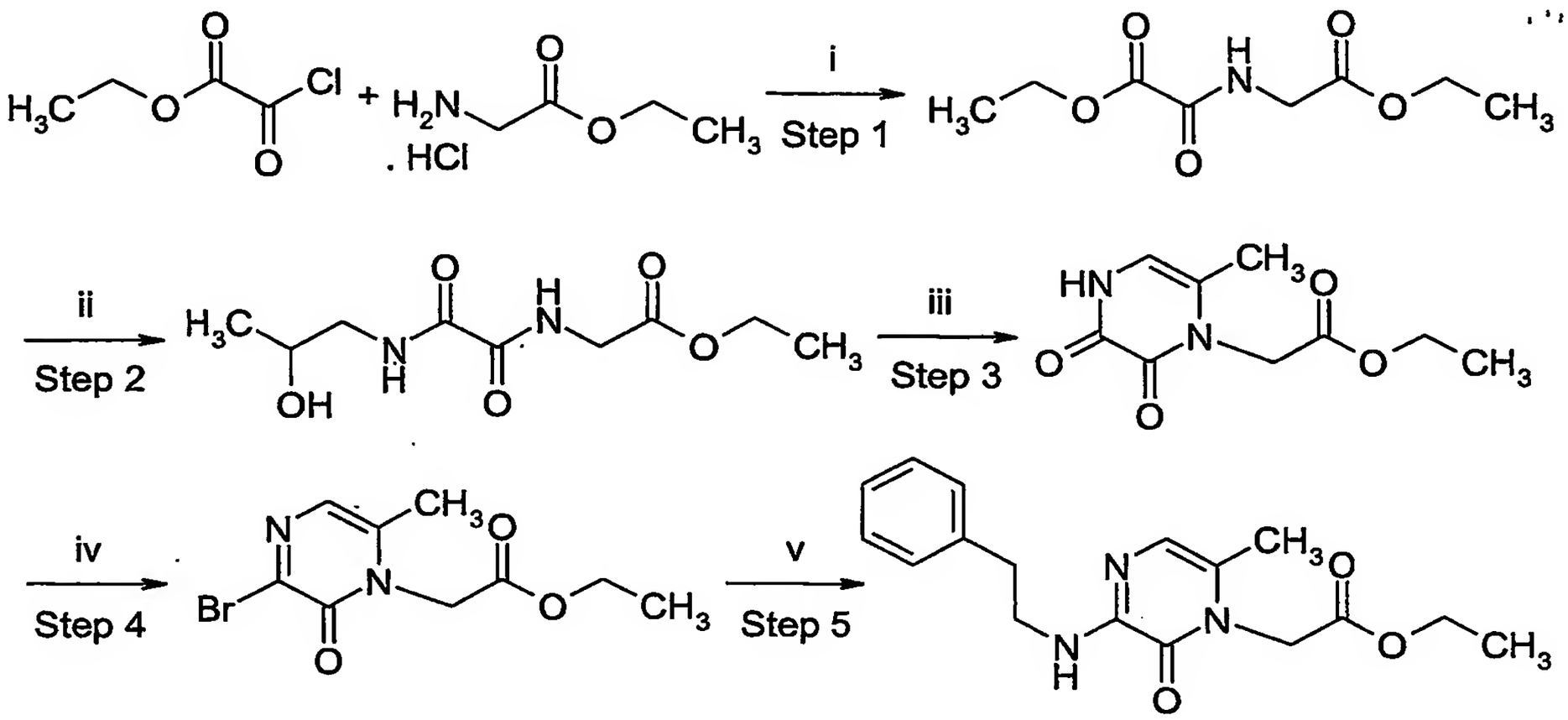


(V)

have been described in the literature. See, e.g. Schemes G through H for general procedures.

A readily scalable synthesis of the 6-methylpyrazinone is described in *Synth. Comm.*; 30; 2000; 3171-3180.

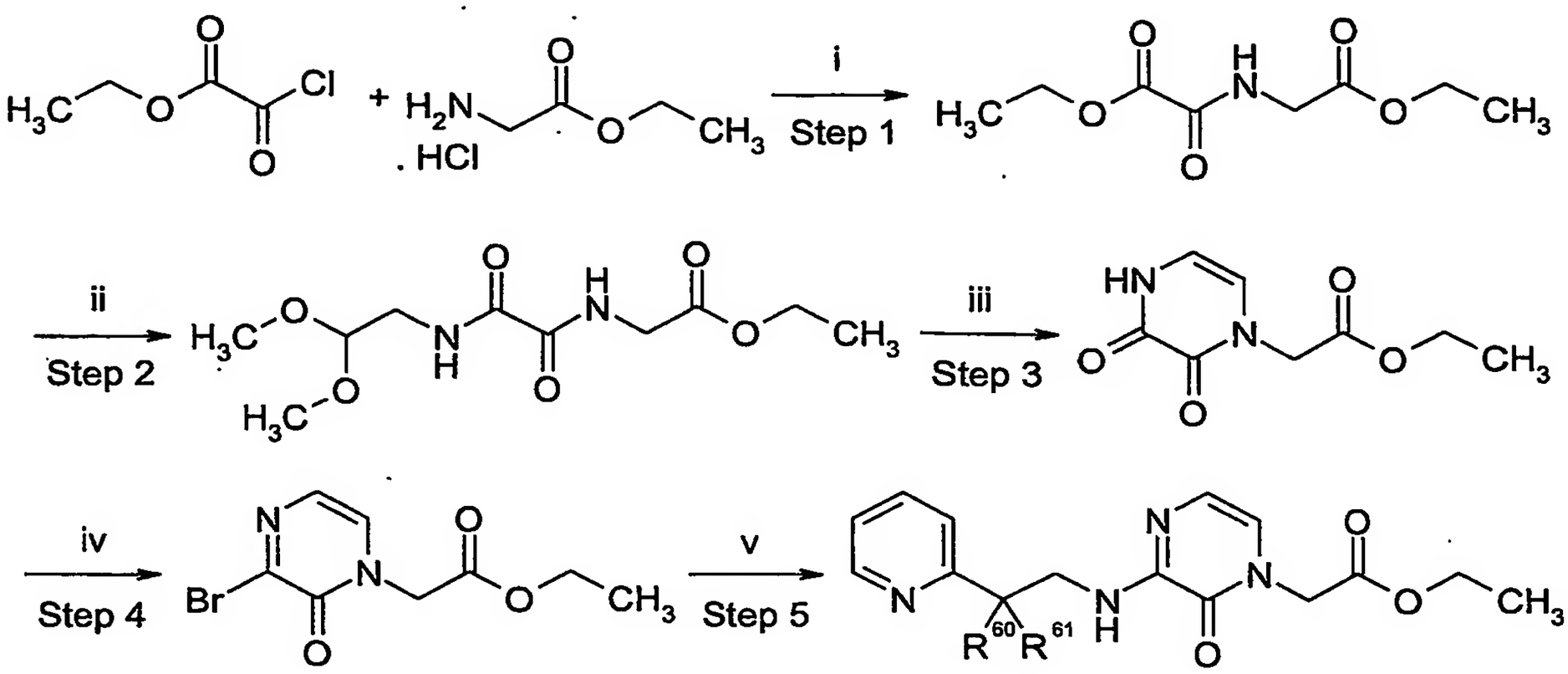
Scheme G



i. Et_3N, DCE, -10 °C; ii. 1-amino-2-propanol, isopropyl acetate; iii. TFA, TFAA, acetic acid, 80 °C; iv. $POBr_3$, DCE, reflux; v. phenethylamine, EtOH, reflux

A modification of the Cheeseman pyrazinedione synthesis may be employed to obtain 1*H*-pyrazin-2-ones as described in *Bioorg. Med. Chem. Lett.*; 13; 2003; 161-164, Scheme H.

Scheme H

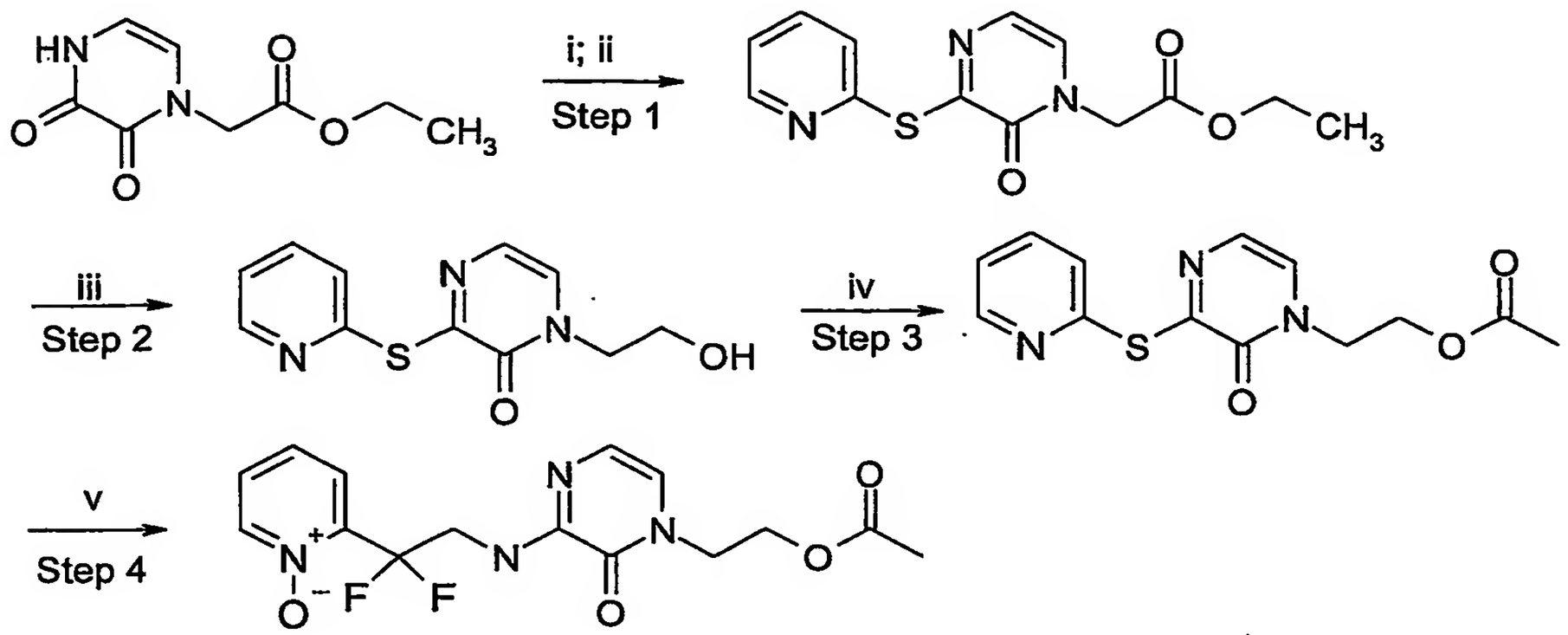


i. Et_3N, DCE, -10 °C; ii. aminoacetaldehyde dimethylacetal, ^iPrOH; iii. acetic acid, HCl, reflux; iv. $POBr_3$, DCE, reflux; v. amine, toluene, EtOH, sealed tube, 120 °C

For both 6-methyl- and 1*H*-pyrazin-2-ones may be possible the synthesis of alternative intermediates with different A-B- residues using a procedure similar to the outlined above but reacting in Step 5 the intermediate bromopyrazin-2-ones with various amines.

In the case of n-oxides pyridines the coupling was performed via activation by pyridylthioimidate and zinc chloride as shown in Scheme I.

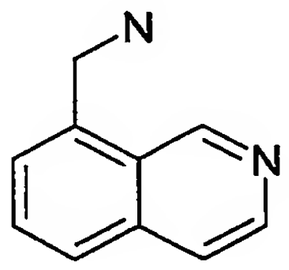
Scheme I



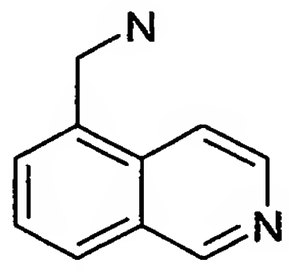
i. oxalyl chloride. AcCN, DMF, 20 °C; ii. mercaptopyridine; iii. $LiBH_4$, iPrOH, -10 °C; iv. acetic anhydide, DCM; v. amine, $ZnCl_2$, AcCN,80 °C

In this case the thioimidate ester was reduced and protected before coupling with the n-oxide pyridine amine.

Amines having the formula (VI) or (VII)



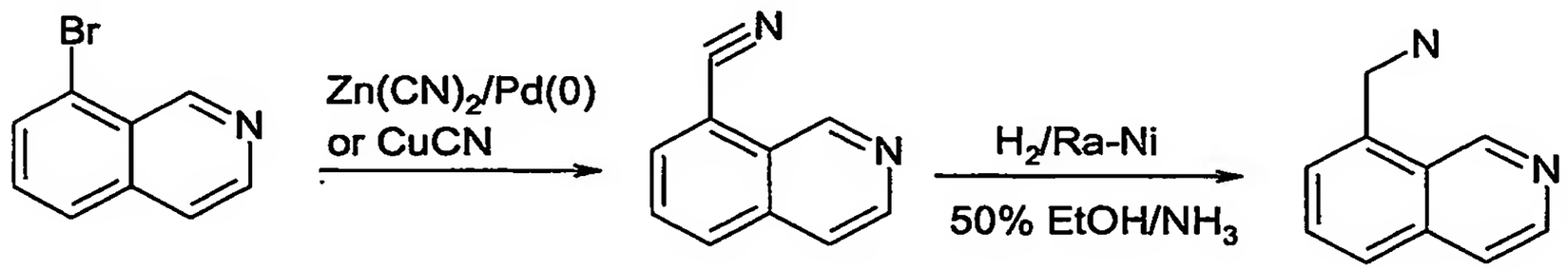
(VI)



(VII)

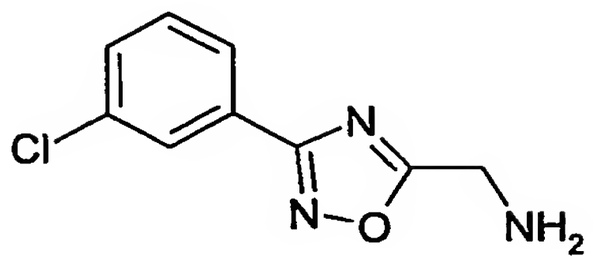
may be conveniently prepared as illustrated in Scheme J for C-isoquinolin-8-yl-methylamine .

Scheme J

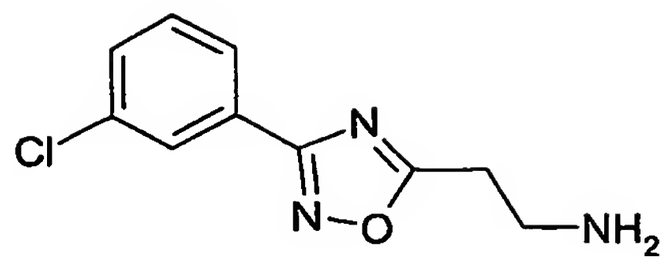


Bromoisoquinoline reacts with copper cyanide or zinc cyanide catalyzed by palladium (0) to yield isoquinolinecarbonitrile, which can be hydrogenated in a Paney-Ni catalyzed reaction to afford C-isoquinolinyl-methylamine.

Amines having the formula (VIII) or (IX)



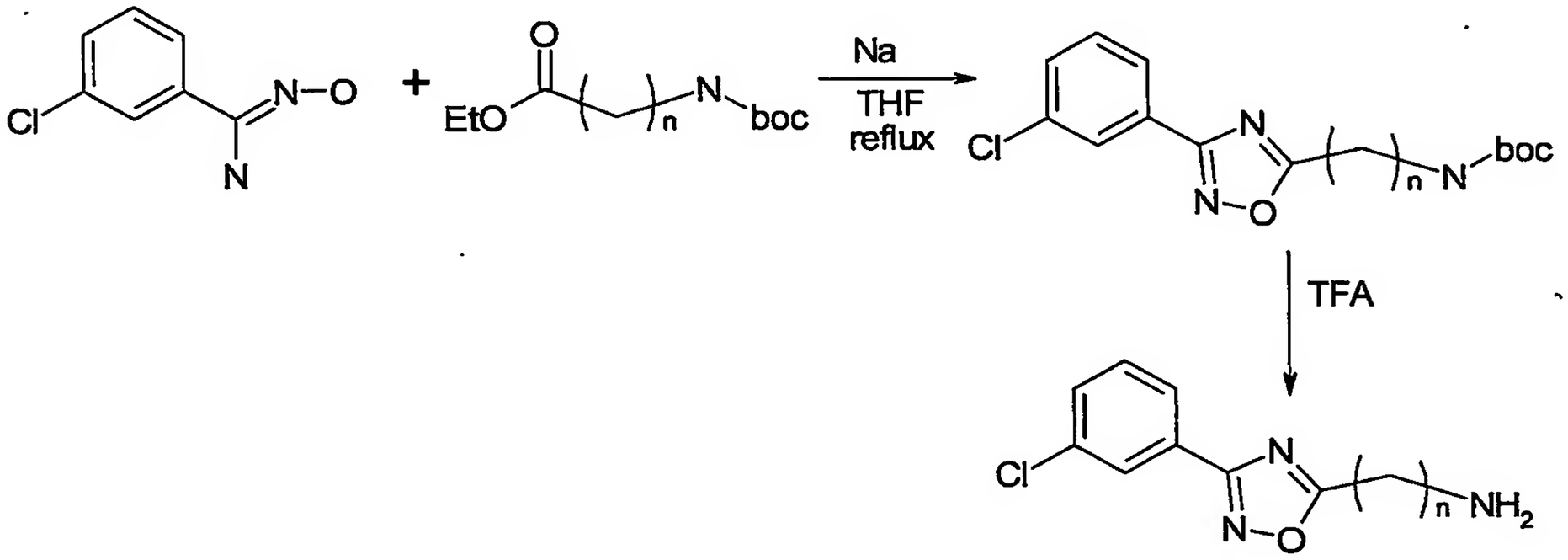
(VIII)



(IX)

may be conveniently prepared as illustrated in Scheme K.

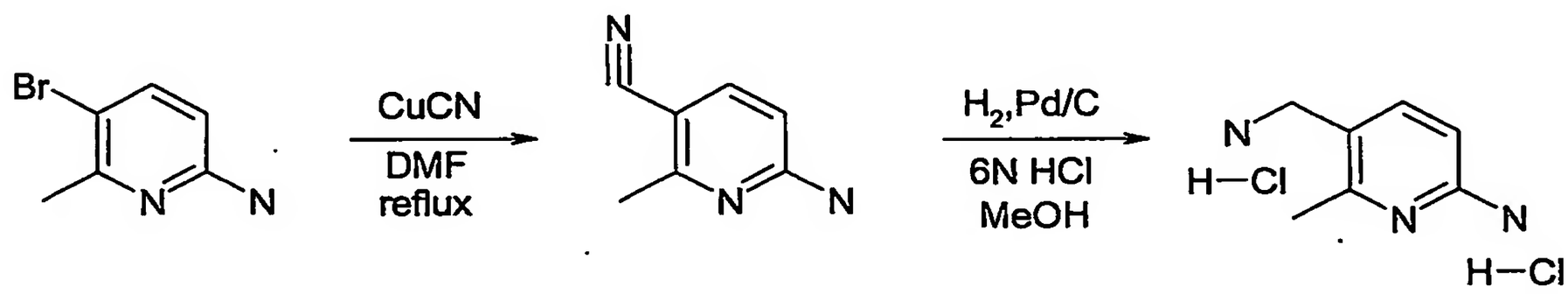
Scheme K



3-Chloro-N-hydroxy-benzamidine cyclizes in presence of sodium hydride with the N-Boc-protected ester to yield the Boc-protected [1,2,4]oxadiazol-5-yl]-methylamine, which can be deprotected with TFA.

5-Aminomethyl-6-methyl-pyridin-2-ylamine may be conveniently prepared as described in *J. Med. Chem.*; 41; 1998; 4466-4474 and illustrated in Scheme L.

Scheme L



5-Bromo-6-methyl-pyridin-2-ylamine reacts with copper cyanide to yield 6-amino-2-methyl-nicotinonitrile, which can be hydrogenated in a Pd catalyzed reaction to afford 5-Aminomethyl-6-methyl-pyridin-2-ylamine as an dihydrochloric salt.

Unless otherwise noted, all nonaqueous reactions were carried out under argon atmosphere with commercial dry solvents. Compounds were purified using flash column chromatography using Merck silica gel 60 (230-400 mesh) or reverse phase preparative HPLC using a Reprosil-Pur ODS3, 5 µm, 20 x 125 mm column with Shimadzu LC8A-Pump and SPD-10Avp UV/Vis diode array detector. The ^{1}H-NMR spectra were recorded on a Bruker AC200 (200 MHz for ^{1}H-NMR) or a Varian VXR-S (300 MHz for ^{1}H-NMR) using d_6-dimethylsulfoxide as solvent; chemical shifts are reported in ppm relative to tetramethylsilane.

Analytical LC/MS was performed using Reprosil-Pur ODS3, 5 µM, 1 x 60 mm columns with a linear gradient acetonitril in water (0.1% TFA) at a flow rate of 250 µl/min. The length of the analytical LC/MS runs, as well as the retention times are given in minutes.

LC/MS (I) runs on a LC10Advp-Pump (Shimadzu) with SPD-M10Avp UV/Vis diode array detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214, 254 and 275 nm.

LC/MS (II) runs on a LC10Advp-Pump (Shimadzu) with SPD-10Avp dual wavelength UV-detector and QP2010 MS-detector in ESI+ modus with UV-detection at 214 and 254 nm.

An LC/MS run with a 10 min linear gradient from 5% to 95% acetonitrile in water, where the compound as a retention time of 1.60 minutes and a m/z of 171, will be reported as follows: LC/MS (I) (5-95%, 10 min): 1.60, 171 (M+1).

In some cases enantiomers were separated by chiral HPLC. The following columns and chromatographic conditions were used:

Analytical:

DAICEL Chiralpak AD-H 4.6mm x 250mm

The eluent (isocratic) was a mixture of n-heptane/EtOH/MeOH in different ratios depending on the compounds. 0.1% DEA was added to the eluent. The flow depends on the eluent and the analytical chiral runs are performed by T = 22°C and p=112 bar (ca. 20 bars postcolumn from MS ESI-capillary).

A analytical chiral run with a mixture of n-heptane/EtOH/MeOH=85:15:0 as eluent with a flow = 0.7 mL/, where the two enantiomers are eluting at 21.3 min and 23.5 min, will be reported as follows: chiral separation (85:15:0, 0.7 mL/min): 21.3 (E1) 23.5 (E2).

The LC/MS system was equipped in the standard analytical set-up, i.e. 2 pumps, mixer and 2µl sample-loop at the injector. Post-column, the semi-micro UV-cell was used and then a ca. 1:2 splitter to achieve a flow to the MS of appr. 300-400 µl/min (ESI+).

Preparative

DAICEL Chiralpak AD-H 20mm x 250mm plus guard-column AD-H 10 mm X 20 mm

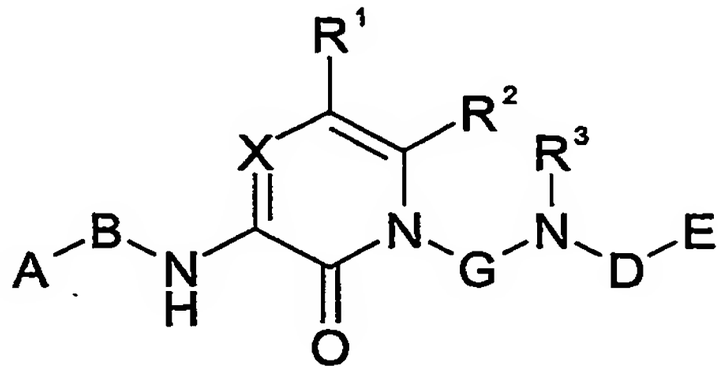
Isocratic n-Heptane/MeOH/EtOH = 15 : 42.5 : 42.5 (0.1% DEA), flow = 12mL/min, T = 22°C, p=99 - 105 bar.

The preparative LC system was equipped only with one pump (pre-mixed solvent), an autosampler with a 2mL loop and on the post-column side a preparative UV-cell and the fraction-collector was installed.

The absolute configuration of the enantiomers was not determined: enantiomer I is the enantiomer with the shorter retention time on the analytical chiral column and enantiomer II is the one with the longer retention time.

General procedure for making compounds of the invention

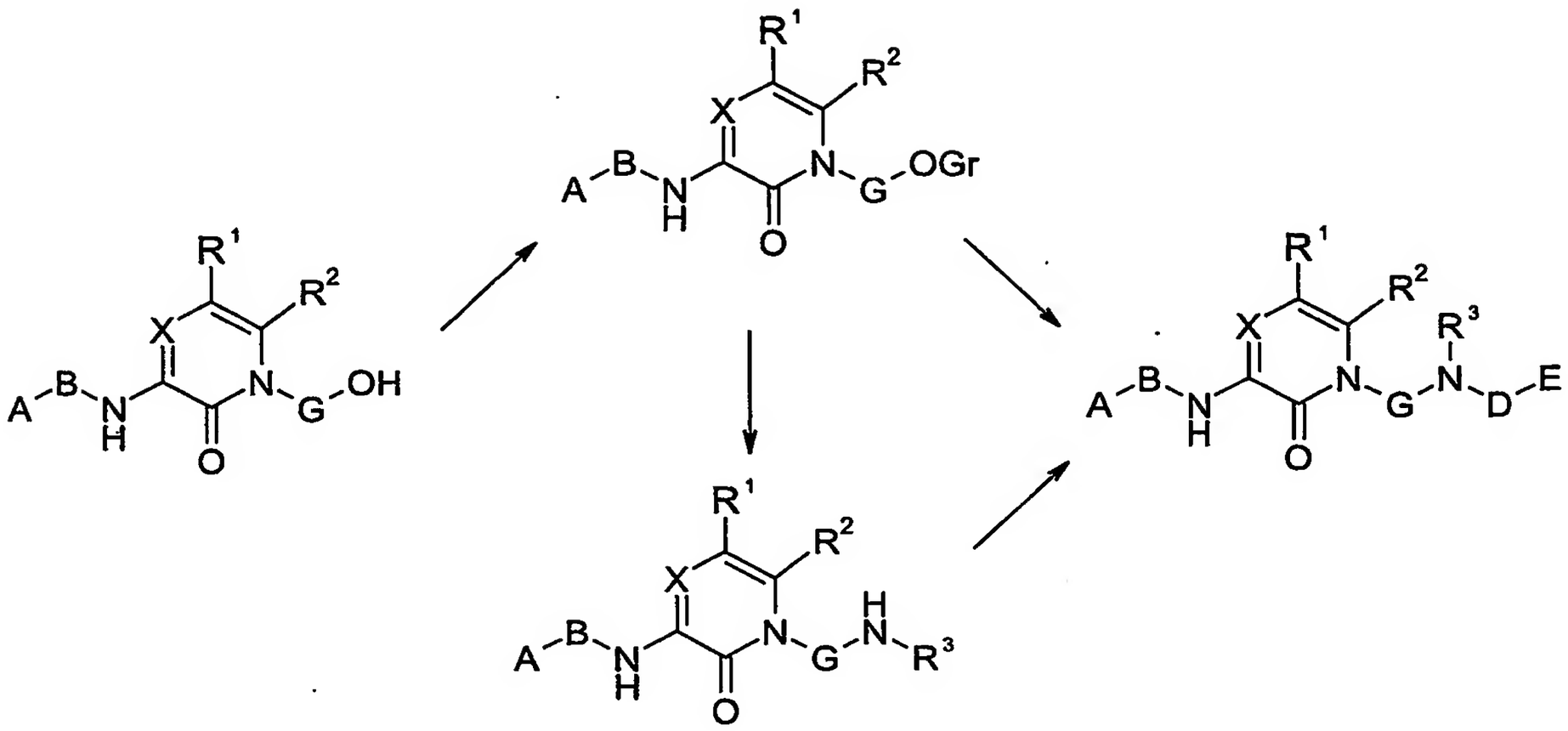
In general, compounds having the structure (I)



(I)

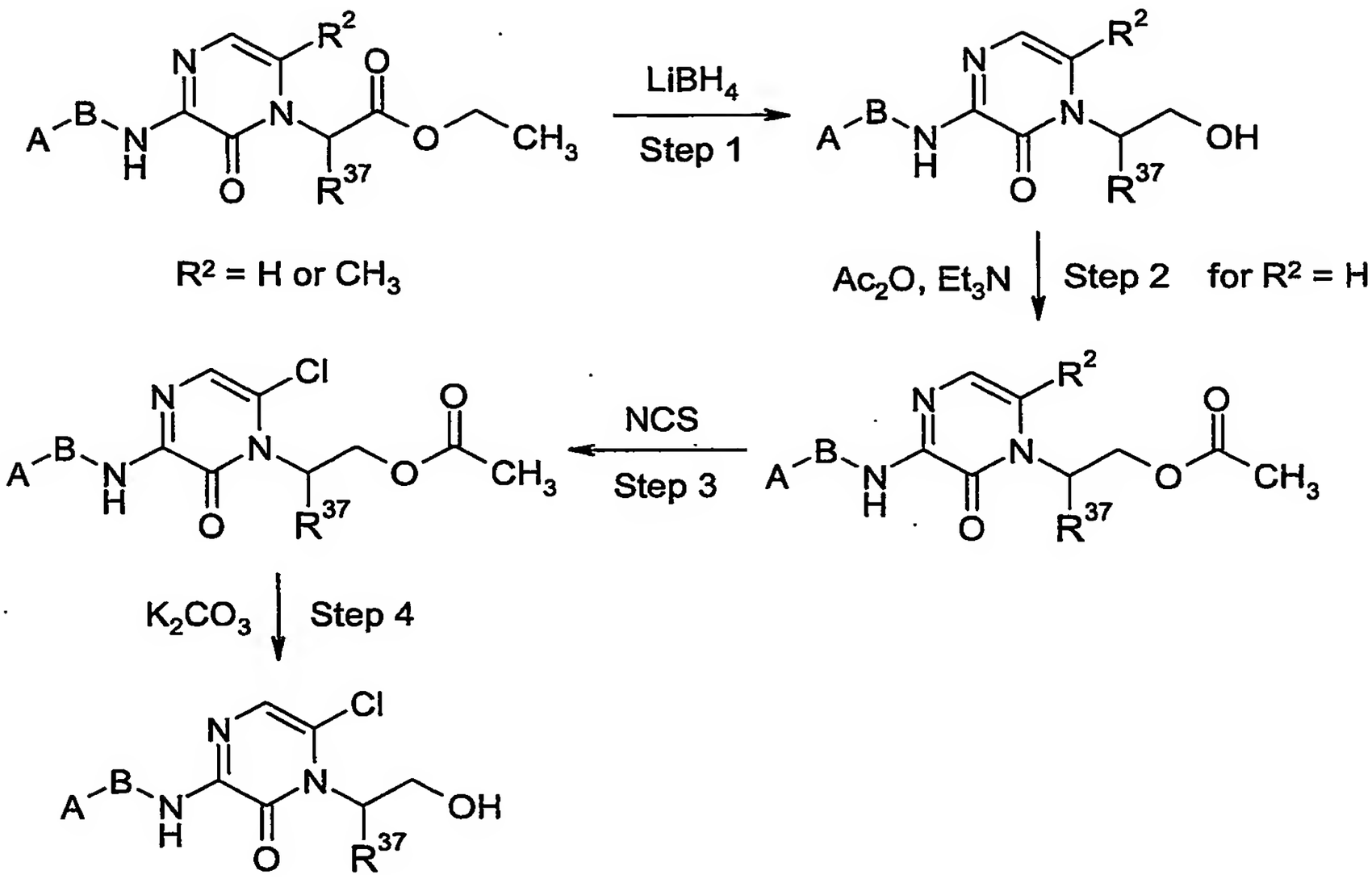
wherein the variables have the above described meanings, may be prepared by a nucleophilic substitution reaction between a substance containing a leaving group (e.g. halogenide, mesylate, tosylate) and a substance containing a nucleophilic group (e.g. amine) or by reductive amination, as shown in Scheme M.

Scheme M



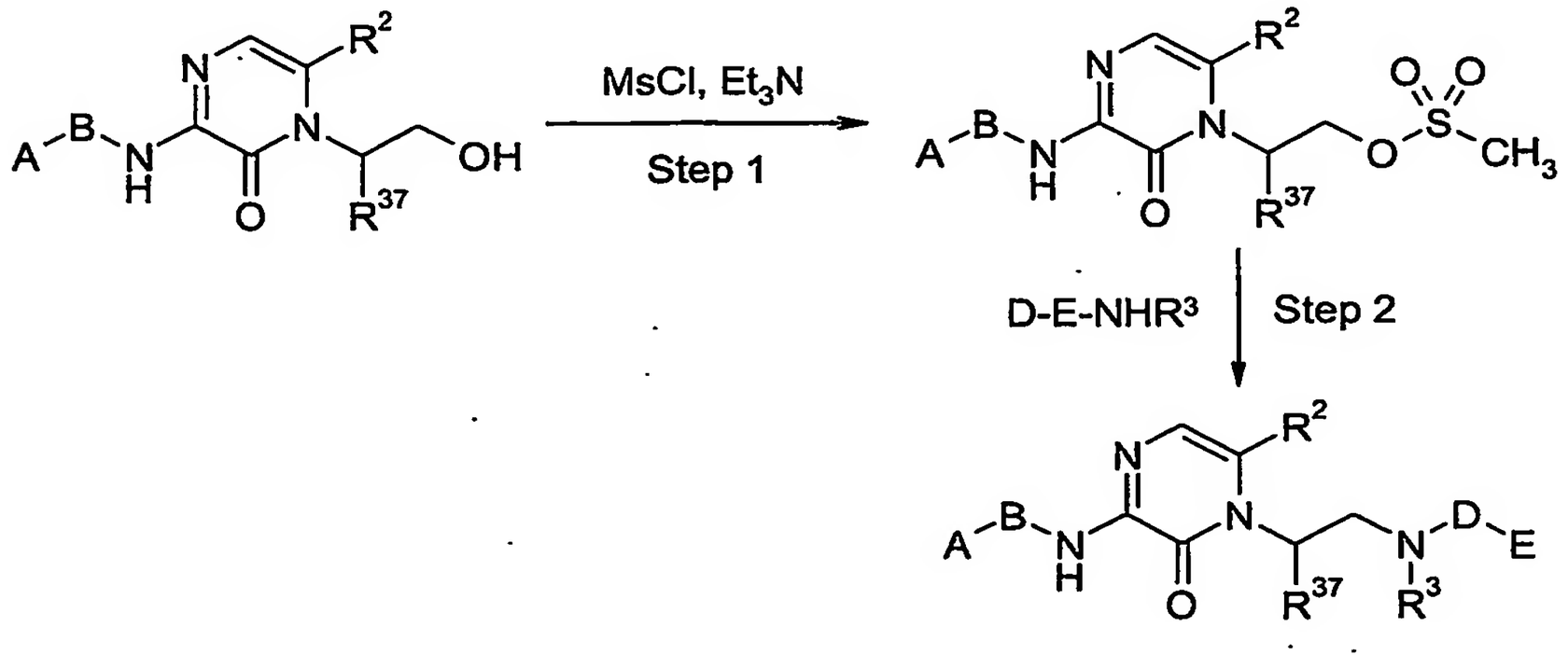
Suitable alcohol starting materials for the synthesis of the claimed compounds may be prepared according to the following procedure. As outlined in Scheme N the starting acetic acid ethyl ester is reduced in Step 1 by lithium borohydride. For the synthesis of the 6-chloro-1*H*-pyrazin-2-ones protection of the resulting alcohol is required in Step 2, e.g. by formation of an acetyl ester. Chlorination with an equimolar amount of *N*-chlorosuccinimide in Step 3 occurs with complete regioselectivity, as described in *J. Med. Chem.*; 46; 2003; 461-473. Hydrolysis of the acetate in Step 4 affords the corresponding alcohol.

Scheme N



Scheme O outlines a procedure for using the alcohol formed according to Scheme N to synthesise compounds that are embodiments of the invention. In Step 1 the starting alcohol is converted into a suitable leaving group, e.g. mesylate, and nucleophilic substitution reaction in Step 2 affords the compounds object of this invention.

Scheme O



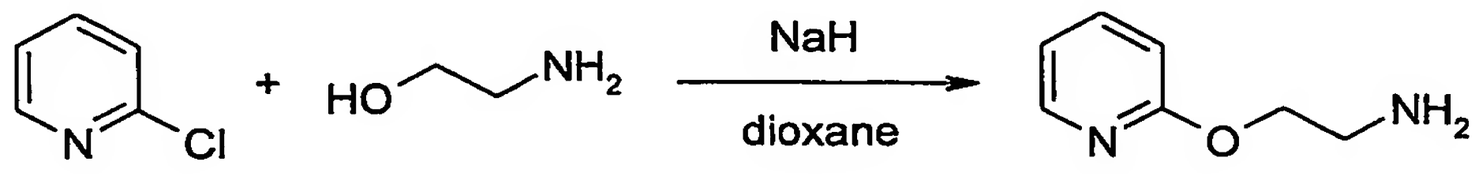
Compounds may be prepared by other means however, and the suggested starting materials and procedures described below are exemplary only and should not be considered as limiting the scope of the invention.

PREPARATIONS

Procedure for making an intermediate according to Scheme A. Only Step 1 may be required in some cases to obtain the desired compounds.

Example 1

Step 1



2-(Pyridin-2-yloxy)-ethylamine. (For synthesis, see *Tetrahedron*; 44; 1998; 91-100)
A mixture of 65 µL (2.11 mmol) and 106 mg (2.64 mmol) of sodium hydride in dioxane is refluxed for 30 min. After cooling of the solution down to room temperature, 200 mg (1.76 mmol) of 2-chloropyridine is added and the mixture is refluxed for 18 h and then concentrated under vacuum. The residue is suspended in water and extracted with dichloromethane. The organic phase is dried with sodium sulfate and concentrated to obtain the title compound as an orange oil, which is used without further purification in the next reaction step.

Example 2

Pyridin-2-yl-ethane-1,2-diamine

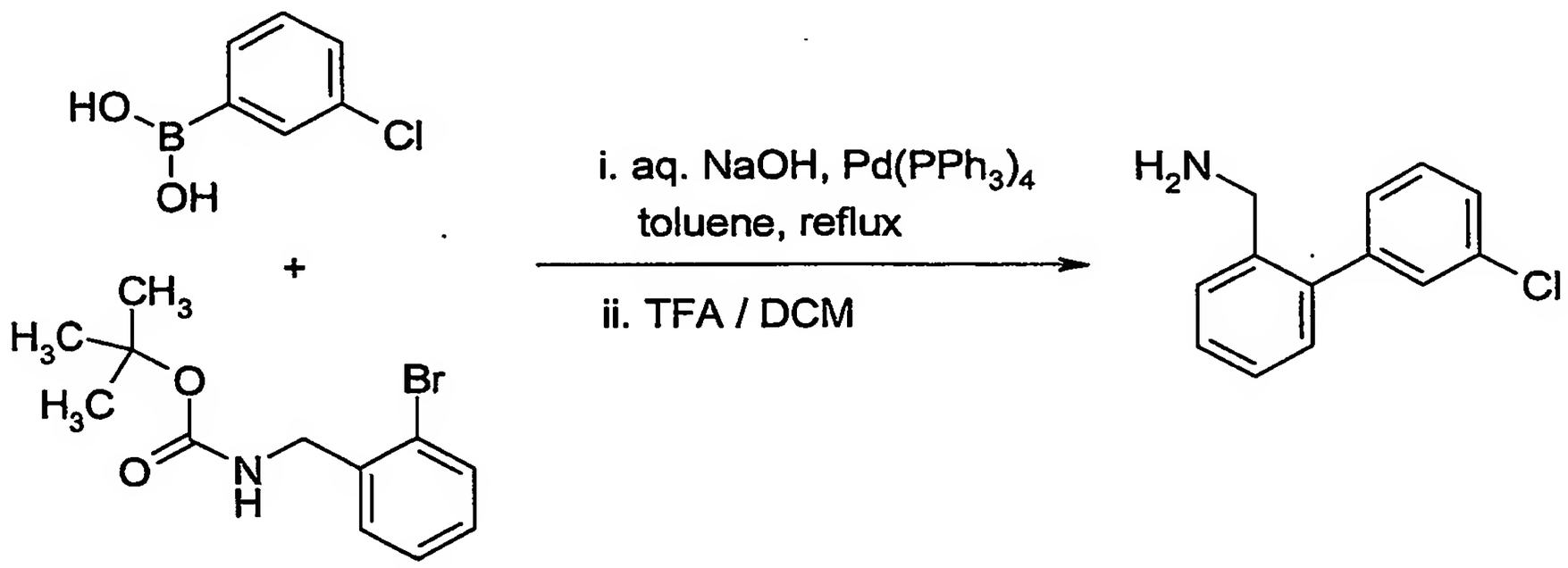
2-Chloropyridine (1.00 g, 8.81 mmol) is dissolved in 10 mL ethylendiamine and the solution is refluxed overnight and then concentrated under vacuum. The residue is dissolved in 10 mL 2M NaOH solution and extracted with chloroform (8 x 10 mL). The organic phase is dried with sodium sulfate and concentrated to obtain the title

compound as an yellow oil, which was used without further purification in the next reaction step.

Example 3

Procedure for making an intermediate according to Scheme B starting from a carbamic acid tert-butyl ester.

Steps 2 and 3

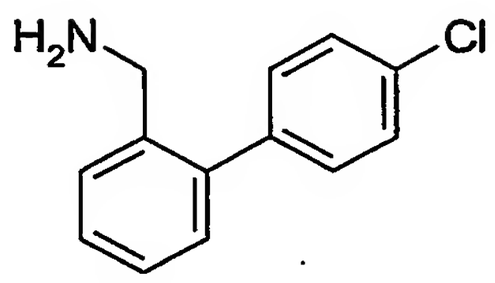


C-(3'-Chloro-biphenyl-2-yl)-methylamine (TFA salt).

To a solution of 90.0 mg (0.580 mmol) of 3-chlorophenylboronic acid in 5 mL of toluene are added 150 µL of water, 430 µL of 5N sodium hydroxide solution, 550 µL of 2-propanol, 26.0 mg (0.022 mmol) of tetrakis(triphenylphosphine)palladium(0) and 148 mg (0.520 mmol) of 2-(bromobenzyl)-carbamic acid tert-butyl ester. The resulting mixture is refluxed under nitrogen for 2 h and then allowed to cool to room temperature. The reaction mixture is diluted with 10 mL of water, transferred to a separatory funnel, and extracted with ether. The organic phase is washed with saturated solution of sodium bicarbonate and brine, dried with sodium sulfate and the solvent is removed under reduced pressure. Purification by flash chromatography (silica gel, eluent: 2% to 5% methanol in dichloromethane) affords 109 mg of (3'-chloro-biphenyl-2-ylmethyl)-carbamic acid tert-butyl ester. The solid is dissolved in 10 mL of dichloromethane, 1.70 mL of trifluoroacetic acid is added and the solution is stirred for 1 h. After evaporation of solvents under reduced pressure, 189 mg (quant.) of the title compound in the form of its trifluoroacetate salt is isolated.

^{1}H-NMR (300 MHz) $\delta = 3.95$ (s, 2H), 7.26-7.59 (m, 8H), 8.13 (bs, 2H).

Example 4



C-(4´-Chloro-biphenyl-2-yl)-methylamine (TFA salt).

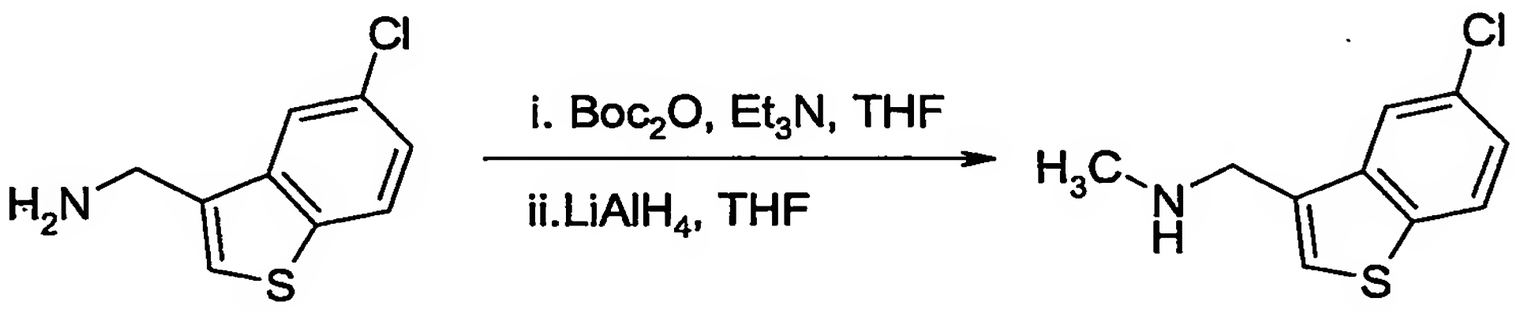
Obtained from 4-chlorophenylboronic acid and 2-(bromobenzyl)-carbamic acid tert-butyl ester using the same procedure outlined for Example 3.

^{1}H-NMR (300 MHz) δ = 3.95 (s, 2H), 7.28-7.61 (m, 8H), 8.18 (bs, 2H).

Example 5

Procedure for making an intermediate according to Scheme C.

Steps 1 and 2



(5-Chloro-benzo[b]thiophen-3-ylmethyl)-methyl-amine.

A solution of 100 mg (0.505 mmol) of C-(5-chloro-benzo[b]thiophen-3-yl)-methylamine, 152 mg (1.11 mmol) of di(*tert*-butoxycarbonyl) and 170 µL (1.21 mmol) of triethylamine in 4 mL of tetrahydrofuran is stirred at room temperature for 4 h. Solvents are removed under reduced pressure, the crude product is dissolved in 5 mL of 1N hydrochloric acid solution and extracted three times with dichloromethane. The organic phase is separated and washed with saturated sodium bicarbonate solution and brine, dried with sodium sulfate and the solvent is removed under vacuum affording 150 mg (quant.) of the (5-chloro-benzo[b]thiophen-3-ylmethyl)-carbamic acid *tert*-butyl ester.

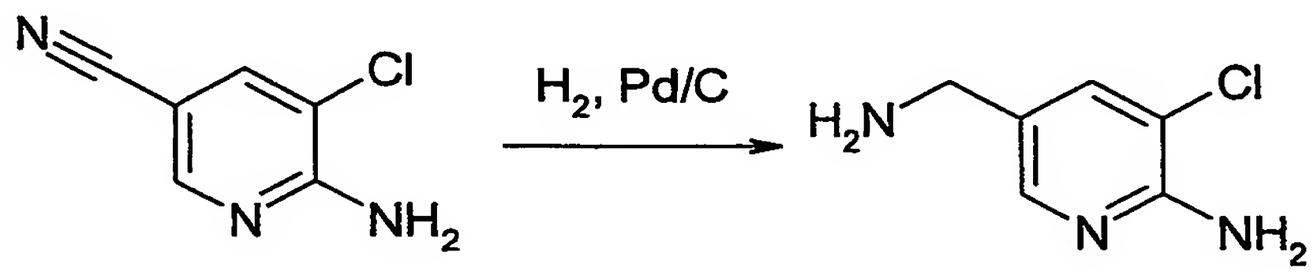
To a solution of 20.0 mg (0.067 mmol) of the carbamic ester in 1 mL of tetrahydrofuran is added 100 µL of a 1M lithium aluminiumhydride solution in tetrahydrofuran. The reaction mixture is stirred at room temperature until gas evolution has ceased and is

further heated at 65 °C for 3 h. After cooling to room temperature, 1N hydrochloric acid solution is added, followed by saturated sodium bicarbonate solution and extraction with dichloromethane. The organic phase is separated, washed with saturated sodium bicarbonate solution and brine, dried with sodium sulfate and concentrated under vacuum to obtain 14.0 mg (quant.) of the title compound.

^{1}H-NMR (300 MHz) $\delta = 3.53$ (s, 2H), 5.94 (s, 2H), 7.51 (s, 1H), 7.78 (s, 1H).

LC/MS (I) (5-95%, 10 min): 2.73, 212 (M+H)

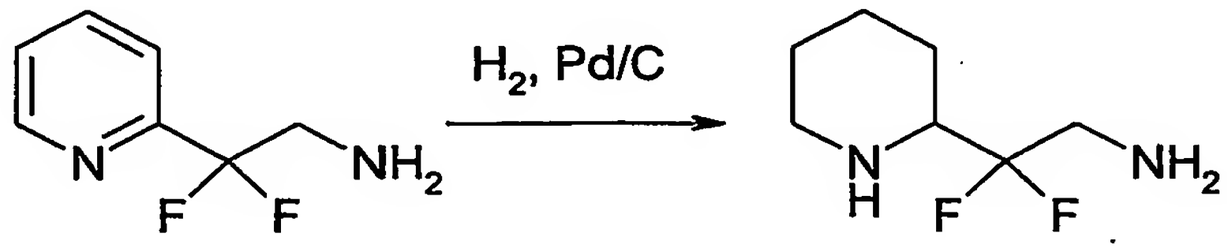
Example 6



5-Aminomethyl-3-chloro-pyridin-2-ylamine dihydrochloride

6-Amino-5-chloro-nicotinonitrile (61.2 mg, 0.40 mmol) is dissolved in ethanol (2.5 mL) and 0.1 mL 6N HCl is added. 10%-palladium on carbon (61.0 mg) is added to the solution and the reaction vessel is purged with hydrogen. The mixture is stirred under hydrogen atmosphere for 5 h at room temperature. The mixture is filtered over celite and the solvent is evaporated under reduced pressure. The product was used in the next step without further purification.

Example 7



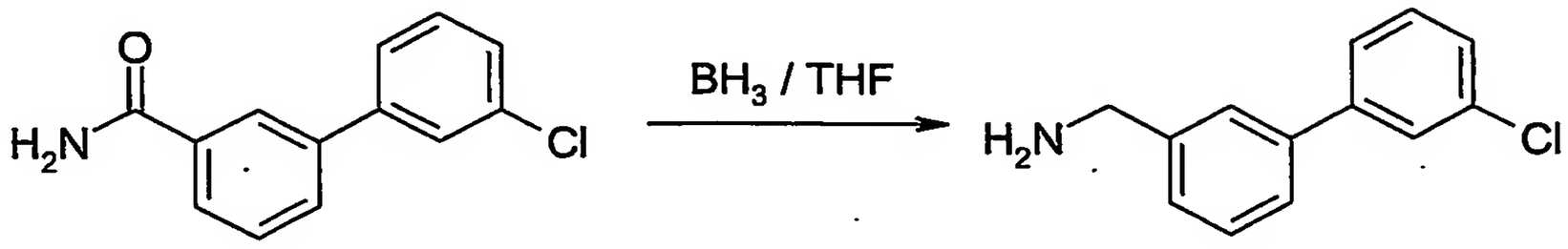
2,2-Difluoro-2-piperidin-2-yl-ethylamine dihydrochlorid salt

Obtained from 2,2-Difluoro-2-pyridin-2-yl-ethylamine using the same procedure outlined for Example 6 and used in the next step without purification.

LC/MS (I) (5-95%, 10 min): 0.21, 165 (M+ H).

Example 8

Procedure for making an intermediate according to Scheme D.



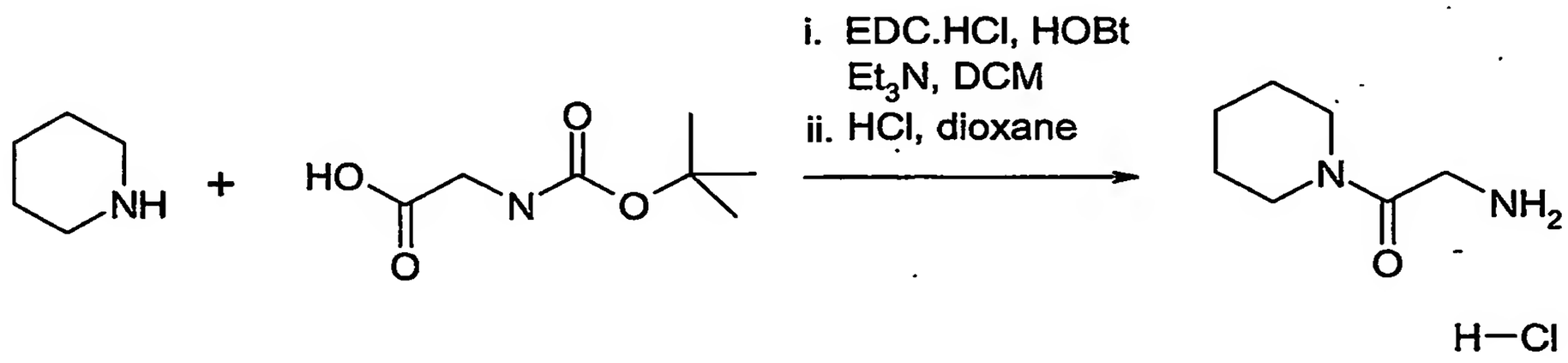
C-(3´-Chloro-biphenyl-3-yl)-methylamine.

To a solution of 30.0 mg (0.129 mmol) of 3'-chloro-biphenyl-3-carboxylic acid amide in 4 mL of tetrahydrofuran is added 3.20 µL of a 1M borane solution in tetrahydrofuran and the resulting mixture is heated at 70 °C overnight. The reaction is quenched with 2 mL of methanol and the solvents are evaporated under reduced pressure. Using preparative HPLC, 20.0 mg (71%) of the title compound is isolated.

LC/MS (I) (5-95%, 10 min): 3.71, 259 ($M+CH_3CN+H$).

Example 9

Steps 1 and 2



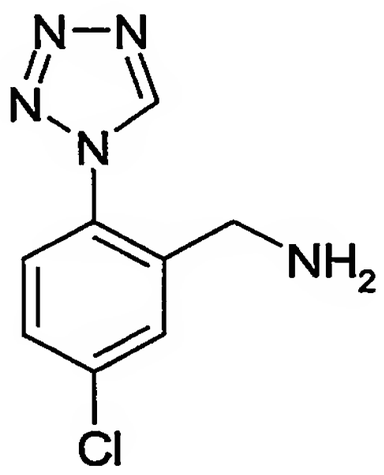
2-Amino-1-piperidin-1-yl-ethanone hydrochloride

To a solution of N-Boc-glycine (400 mg, 2.28 mmol) and hydroxybenzotriazole (463 mg, 3,43 mmol) in 10 mL of dichloromethane are added piperidine (233 mg, 2.74 mmol), Et_3N (796 µL, 5.71 mmol) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (524 mg, 2.74 mmol). The resulting mixture is stirred at room temperature for 17 h and then washed with saturated sodium bicarbonate solution, water and brine. The organic phase is dried over sodium sulfate and the solvent is

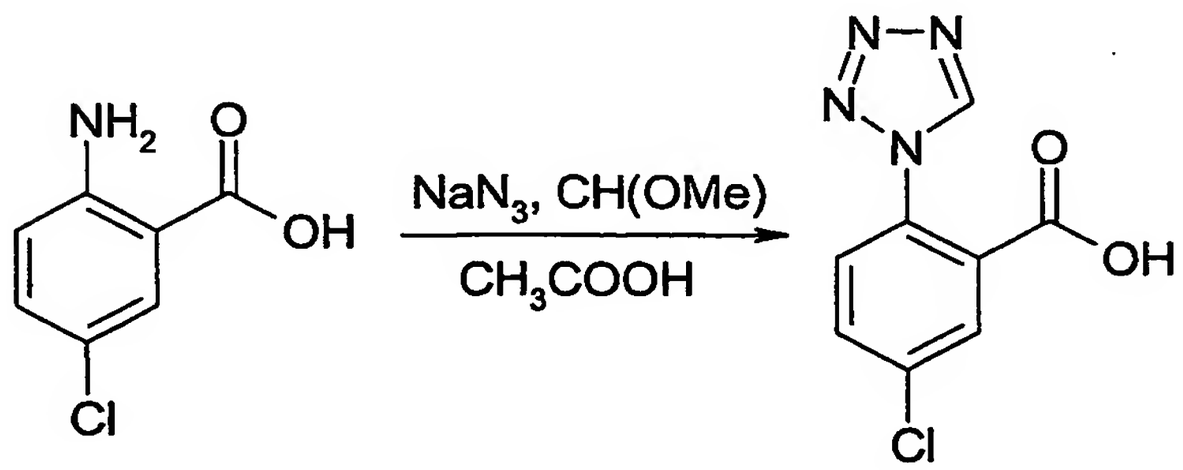
evaporated under reduced pressure. After column chromatography (MeOH:DCM= 2:98) the product is isolated in 80% yield.

(2-Oxo-2-piperidin-1-yl-ethyl)-carbamic acid tert-butyl ester (440 mg, 1.82 mmol) is dissolved in dioxane (10 mL) under an argon atmosphere and 5 mL of a 4 M hydrochloric acid solution in dioxane are added. The solution is stirred for 3 h at room temperature, the solvent is evaporated under reduced pressure and the crude material is purified by column chromatography (DCM : MeOH (with1 % of a 10% NH_3 in water) = 95 :5) to give 166 mg (1.17 mmol, 64%) of 2-amino-1-piperidin-1-yl-ethanone hydrochloride.

Example 10



Step 1



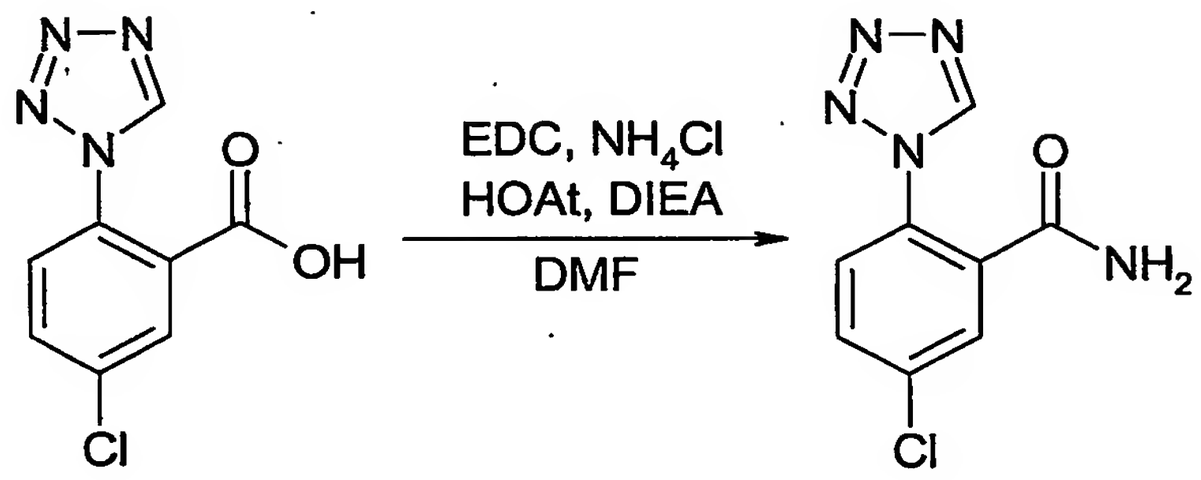
5-chloro-2-tetrazol-1-yl-benzoic acid (For synthesis, see *J. Med. Chem.*; *47*; 2004; 2995-3008)

A suspension of 2-amino-5-chlorobenzoic acid (1.00 g, 5.83 mmol), trimethylorthoformate (2.00 mL, 18.0 mmol), and sodium azide (1.13 g, 17.5 mmol) in glacial acetic acid (25 mL) is stirred at room temperature for 2 h. Filtration and concentration from toluene gives 5-chloro-2-tetrazol-1-yl-benzoic acid (940 mg, 72%).

^{1}H-NMR (300 MHz) δ = 7.71-7.74 (m, 1H), 7.86-7.90 (m,1H), 8.00-8.02 (m, 1H), 9.73 (s, 1H).

LC/MS (I) (5-95%, 10 min): 2.88, 225 (M+H).

Step 2



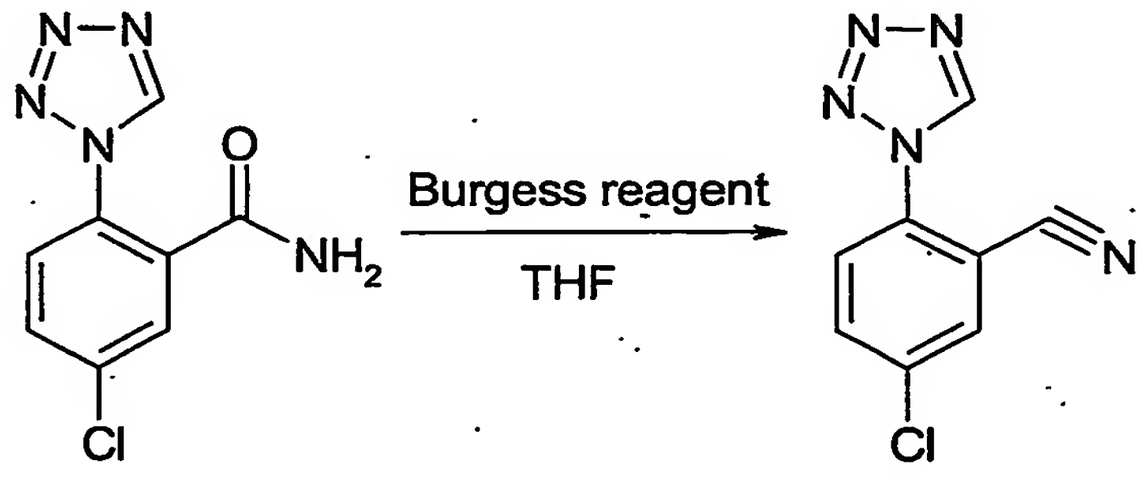
5-chloro-2-tetrazol-1-yl-benzamide

A solution of 5-chloro-2-tetrazol-1-yl-benzoic acid (1.0 g, 5.2 mmol), ammonium chloride (0.56 g, 10.4 mmol), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.0 g, 10.4 mmol), 1-hydroxy-7-azabenzotriazole (1.99 g, 10.4 mmol), and diisopropylethylamine (3.1 mL, 20.8 mmol) in DMF (15 mL) is stirred at room temperature overnight. Water is added, and the reaction mixture is extracted with ethyl acetate. The combined organic layers are washed with brine. Drying and solvent evaporation gives 5-chloro-2-tetrazol-1-yl-benzamide (540 mg, 46%).

^{1}H NMR (d6-DMSO, 300 MHz) δ = 7.56 (s, 1H), 7.68-7.79 (m, 2H), 8. 03 (s, 1H), 9.62 (s, 1H).

LC/MS (I) (5-95%, 10 min): 1.63, 224 (M+H).

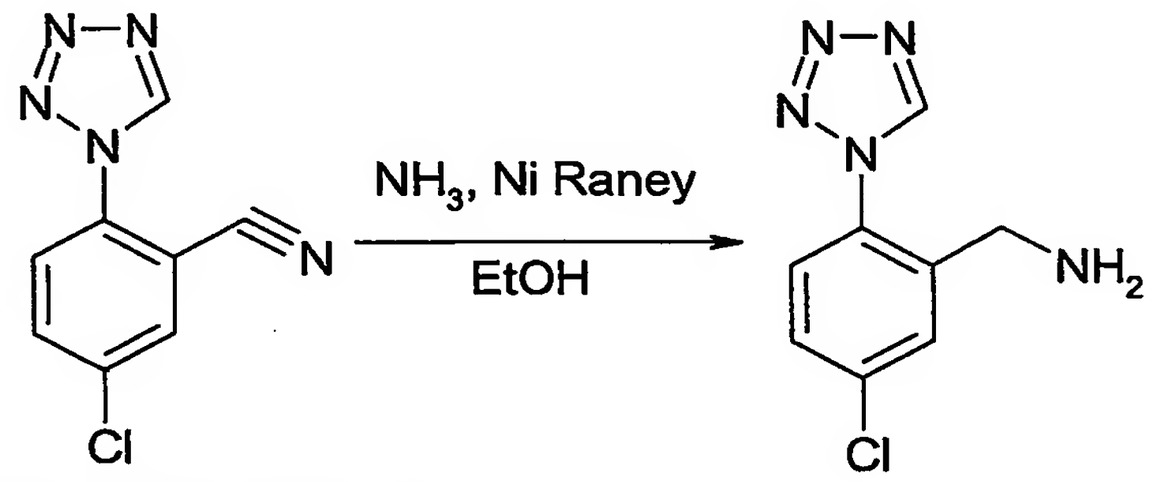
Step 3



5-chloro-2-tetrazol-1-yl-benzonitrile

To a solution of 5-chloro-2-tetrazol-1-yl-benzamide (100 mg, 0.49 mmol) in THF (5 mL) is added (methoxycarbonylsulfamoyl)-ammonium hydroxide (186 g, 0.79 mmol). After stirring 2 h at room temperature water is added, and the reaction mixture is extracted with ethyl acetate. The combined organic layers are washed with brine. Drying and solvent evaporation gives 5-chloro-2-tetrazol-1-yl-benzonitrile (38 mg, 0.185 mmol).
LC/MS (II) (5-70%, 10 min): 3.72, 206 (M+H).

Step 4



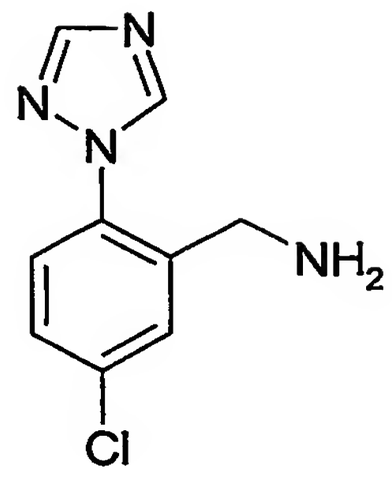
5-chloro-2-tetrazol-1-yl-benzylamine

A solution of 5-chloro-2-tetrazol-1-yl-benzonitrile (38 mg, 0.185 mmol) in ethanol saturated with ammonia (125 mL) is stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere overnight. The reaction mixture is filtered over Celite and concentrated to give 5-chloro-2-tetrazol-1-yl-benzylamine which is purified by HPLC to give 20 mg (58%) of the TFA-salt.

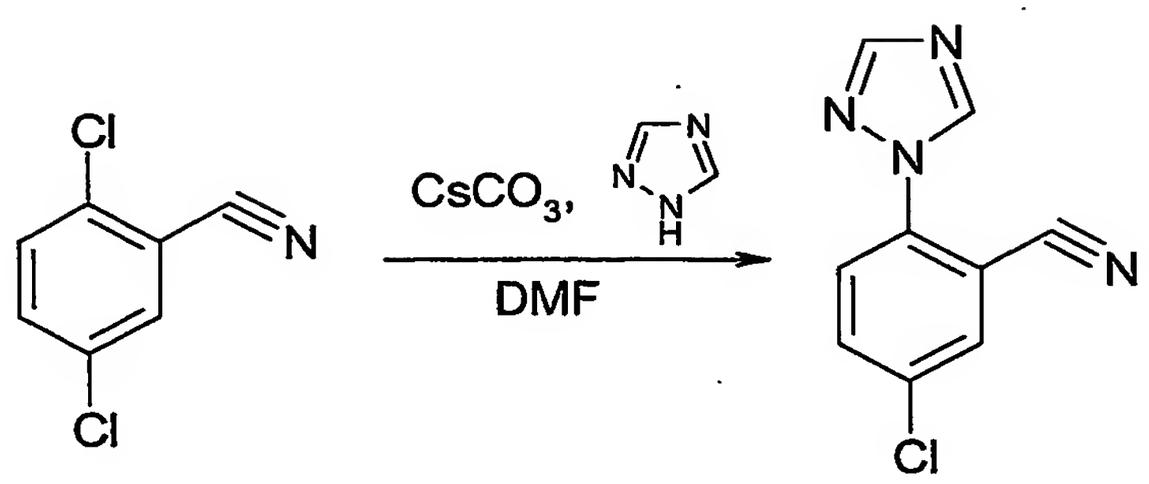
^{1}H NMR (d6-DMSO, 300 MHz) δ = 3.99 (s, 2H), 7.65-7.80 (m, 2H), 7.82-7.86 (m, 1H), 9.82 (s, 1H).

LC/MS (I) (5-70%, 10 min): 2.05, 210 (M+H).

Example 11



Step 1

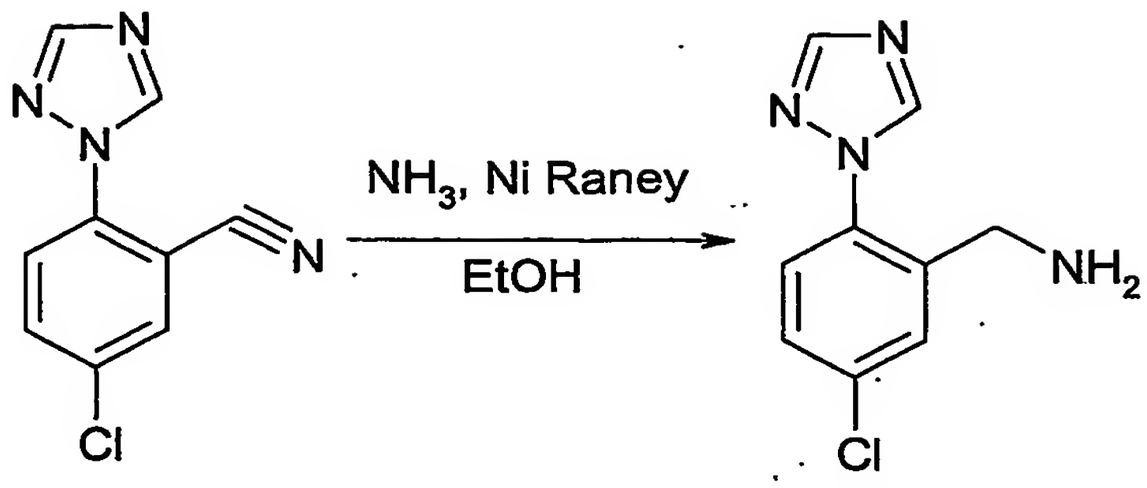


5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (For synthesis, see *J. Med. Chem.*; *47*; 2004; 2995-3008)

To a solution of 2,5-dichlorobenzonitrile (1.00 g, 5.81 mmol) in DMF (10 mL) are added cesium carbonate (2.27 g, 6.98 mmol) and 1,2,4-triazole (482 mg, 6.98 mmol). The reaction mixture is stirred at 85 °C for 16 h and 100 °C for 8 h. The reaction is diluted with water and extracted with ethyl acetate. The combined organic layers are washed with aqueous lithium chloride, dried, and concentrated to give 5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (1.12 g, 5.47 mmol). The crude product is used in the next step without further purification.

LC/MS (I) (5-95%, 10 min): 3.00, 205 (M+H).

Step 2

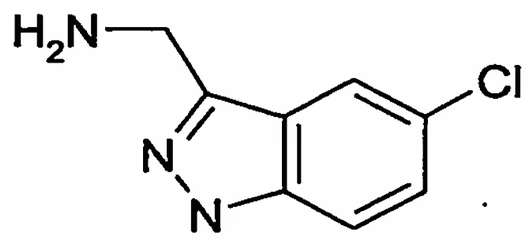


5-chloro-2-[1,2,4]triazol-1-yl-benzylamine

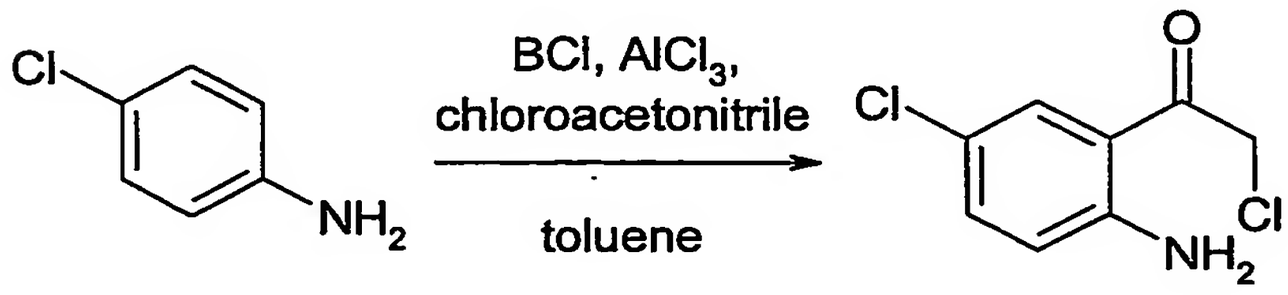
A suspension of 5-chloro-2-[1,2,4]triazol-1-yl-benzonitrile (500 mg, 2.42 mmol) in ethanol saturated with ammonia (20 mL) is stirred in the presence of Raney nickel (50% slurry in water, washed with ethanol, catalytic amount) under a hydrogen atmosphere for 26 h. The reaction mixture is filtered over Celite and concentrated. Purification by flash chromatography (silica gel, eluent = 2% to 10 % DCM (with 10% ammonium hydroxide) in methanol) gives 5-chloro-2-[1,2,4]triazol-1-yl-benzylamine (324 mg, 64%). ^{1}H NMR (d6-DMSO, 200 MHz): 3.54 (s, 2H), 7.43 (m, 2H), 7.73 (m,1H), 8.18 (s, 1H), 8.60 (s, 1H).

LC/MS (I) (5-70%, 10 min): 2.06, 209 (M).

Example 12



Step 1



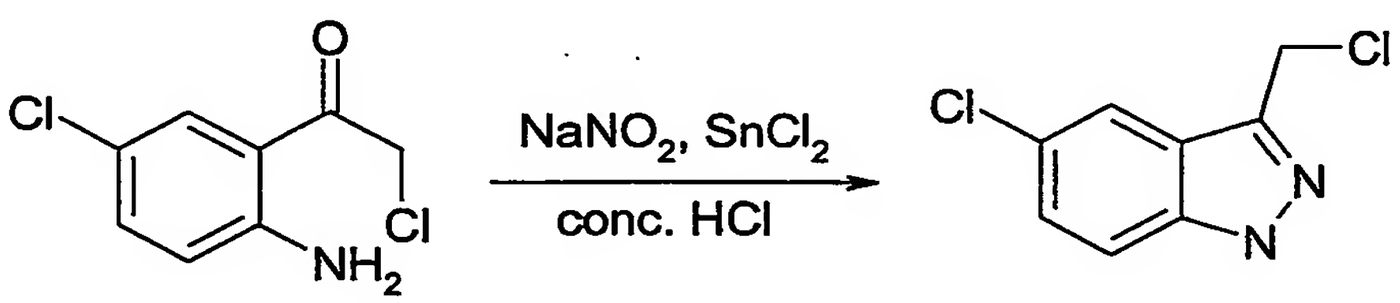
5-chloro-2-amino-a-chloroacetophenone

To a stirred solution of boron trichloride (8,62 mL of 1 M solution in heptane) in dry benzene (5 mL), a solution of 4-chloroaniline (1,00 g, 7,84 mmol) in dry benzene (15

mL) is added dropwise under icecooling. To the resulting mixture containing 4-chloroaniline borontrichloride complex, chloroacetonitrile (0.60 mL, 9,41 mmol) and aluminiumtrichloride (1,15 g, 8,62 mmol) are added successively. The mixture is then refluxed for 6 h under nitrogen, becoming a solution of two layers. The evolved hydrogen chloride is absorbed through a drying tube containing silica gel or calcium chloride to a surface of aqueous sodium hydroxide. After cooling, ice 2 N hydrochloric acid is added and a yellow precipitate is formed. To hydrolyze the ketimine of 5-chloro-2-amino-a-chloroacetophenone, the mixture is warmed at 80 °C under stirring, until the precipitate has dissolved (ca. 30 min). The cooled mixture is extracted with chloromethane (three times) and the organic layer is washed with water, dried with sodium sulfate, and concentrated. The neutral fraction obtained (1,00 g) is recrystallized to obtain 680 mg (3,33 mmol, 43% yield) of pure 5-chloro-2-amino-a-chloroacetophenone.

LC/MS (I) (5-95%, 5 min): 2.77, 245 (M+H+AcCN).

Step 2

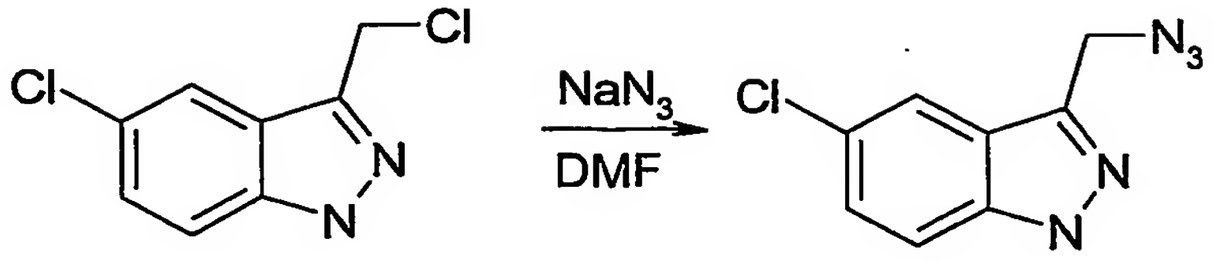


5-chloro-3-(chloromethyl)-1H-indazole

To a stirred suspension of 2-amino-5-chloro-α-chloroacetophenone (670 mg, 3,28 mmol) in conc. hydrochloric acid (10 mL) is added a solution of sodium nitrite (250 mg, 3,61 mmol) in water (2 mL) while mantaining the reaction temperature at 0 °C. After 1 h a solution of $SnCl_2 \bullet 2H2O$ (1,78 g, 7,87 mmol) in conc. hydrochloric acid (5 mL) is added to the reaction mixture, which is then stirred at the same temperature for 1 h. Next, ice water is added to the reaction mixture. The precipitate is collected by filtration, washed with water and .dried giving crude 5-chloro-3-(chloromethyl)-1H-indazole (370 mg, 1,84 mmol, 56% yield) which is used in the next step without further purification.

LC/MS (I) (5-95%, 5 min): 2.67, no mass peak.

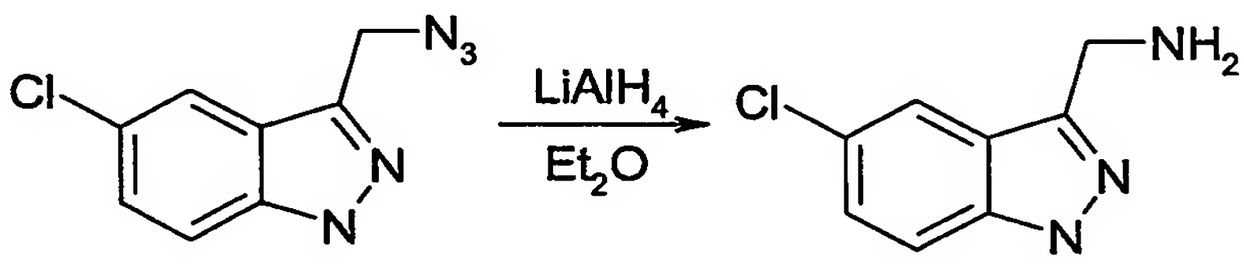
Step 3



3-(azidomethyl)-5-chloro-1H-indazole

A stirred solution containing 5-chloro-3-(chloromethyl)-1H-indazole (370 mg, 1,84 mmol) , sodium azide (156 mg, 2,40 mmol), water (0,5 mL) and DMF (5,00 mL) is warmed at 90 °C for 1 h and then the mixture is concentrated under reduced pressure. Ice is added and the resulting precipitate is collected by filtration and washed with water giving 330 mg (1,59 mmol, 85% yield) of 3-(azidomethyl)-5-chloro-1H-indazole.
LC/MS (I) (5-95%, 5 min): 2.63, 249 (M+H+AcCN).

Step 4

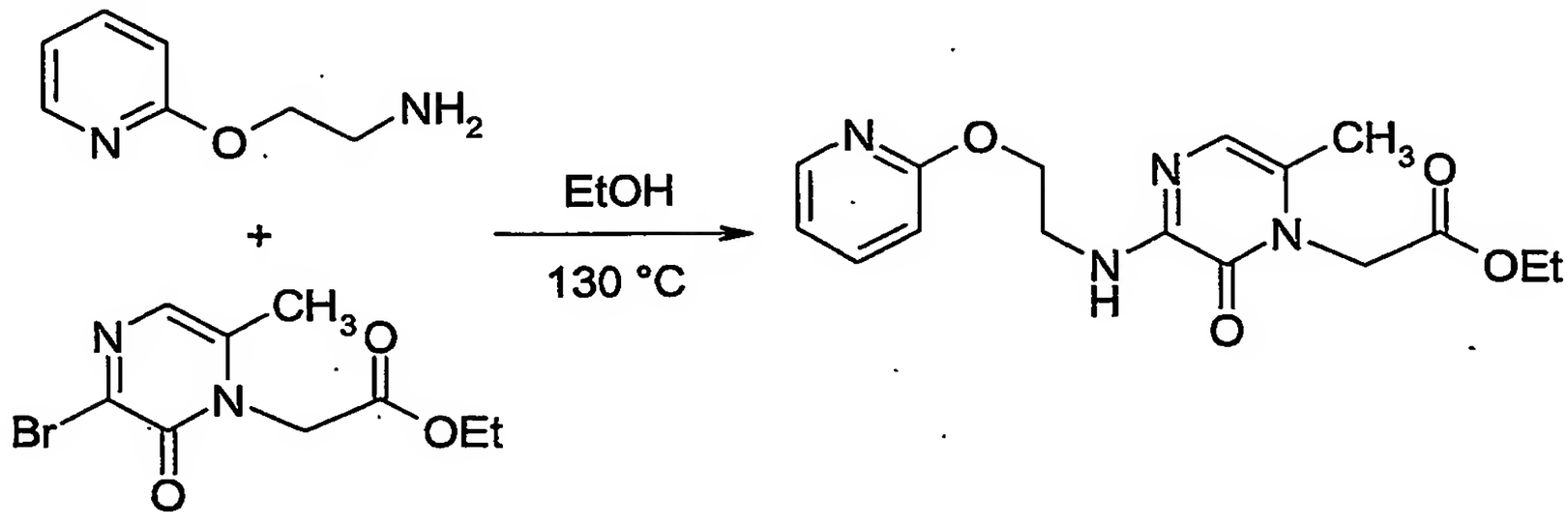


3-(aminomethyl)-5-chloro-1H-indazole

To a stirred 1M THF-solution of $LiAlH_4$ (5,00 mL) is added a solution of 3-(azidomethyl)-5-chloro-1H-indazole (330 mg ,1,59 mmol) in Et_2O (10 mL) dropwise at room temperature, and the mixture is refluxed for 1 h. After quenching the excess of $LiAlH_4$ with wet Et_2O, the precipitate is filtered off and washed with DCM-EtOH (9:1), giving crude 3-(aminomethyl)-5-chloro-1H-indazole. The purification by column chromatography (silica gel, eluent = 10% DCM in methanol with 0.1 % Et_3N) affords 105 mg (0,58 mmol, 37%) of pure material. ^1H NMR (d6-DMSO, 200 MHz): 4.01 (s, 2H), 7.25-7.28 (m, 1H), 7.43-7.47 (m,1H), 7.92-7.93 (m, 1H).
LC/MS (I) (5-95%, 5 min): 1.59, 182 (M+H).

Example 13

Procedure for making an intermediate according to Scheme G, Step 5.

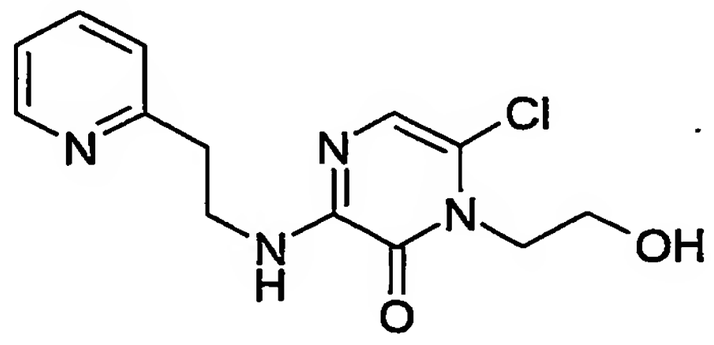


{6-Methyl-2-oxo-3-[2-(pyridin-2-yloxy)-ethylamino]-2*H*-pyrazin-1yl}-acetic acid ethyl ester.

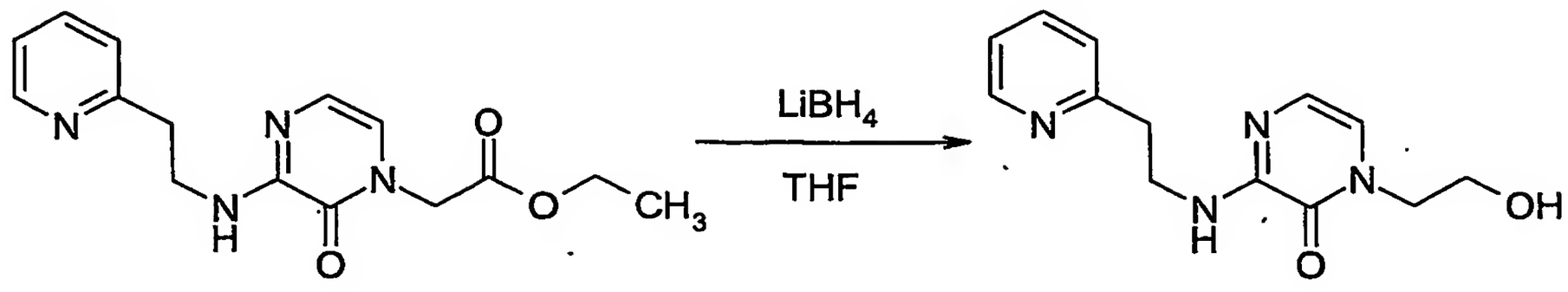
A solution of 70.0 mg (0.254 mmol) of (3-bromo-6-methyl-2-oxo-2*H*-pyrazin-1-yl)-acetic acid ethyl ester (for preparation see *Synth. Comm.*; 30; 2000; 3171-3180) and 85.2 mg (0.560 mmol) of 2-(pyridin-2-yloxy)-ethylamine in 5 mL of ethanol is heated overnight at 130 °C in a sealed tube. After allowing to cool down, the solution is diluted with 10 mL of water and then extracted three times with ethyl acetate. The organic phase is separated, dried with sodium sulfate and the solvent is removed under reduced pressure. The crude mixture is purified using flash chromatography (silica gel, eluent: 50% ethyl acetate in cyclohexane) to afford 22.0 mg (26%) of the title compound.
LC/MS (I) (5-95%, 10 min): 2.40, 333 (M+H).

Example 14

Procedure for making an intermediate according to Scheme N.



Step 1



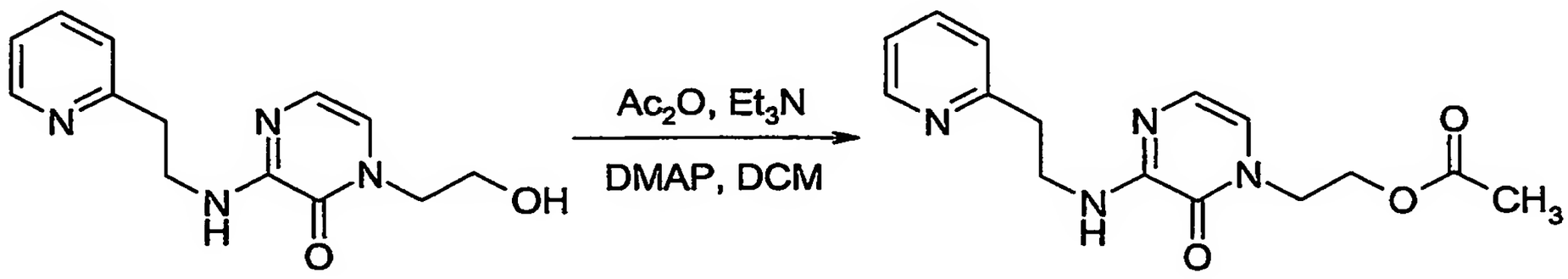
1-(2-Hydroxy-ethyl)-3-(2-pyridin-3-yl-ethylamino)-1*H*-pyrazin-2-one.

To a solution of 1.00 g (3.31 mmol) of [2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-acetic acid ethyl ester (see *J. Med. Chem.*; 46; 2003; 461-473 for synthesis) in 33 mL of tetrahydrofuran is added 1.65 mL (3.31 mmol) of a 2M lithium borohydride solution in tetrahydrofuran and the resulting mixture is stirred for 3 h at room temperature. After addition of 20 mL of methanol the mixture is stirred until gas evolution has ceased. The solvent is evaporated under reduced pressure and the crude product is dissolved in methanol and refluxed for 1 h. The solvent is removed under reduced pressure and the title product (861 mg, quant.) is taken directly onto the next step.

^{1}H-NMR (300 MHz) δ = 2.97-3.04 (m, 2H), 3.57-3.67 (m, 4H), 3.81-3.87 (m, 2H), 4.84-4.90 (m, 1H), 6.72 (s, 2H), 7.12-7.29 (m, 3H), 7.66-7.74 (m, 1H), 8.48-8.50 (m, 1H).

LC/MS (I) (5-95%, 10 min): 1.32, 261 (M+H).

Step 2

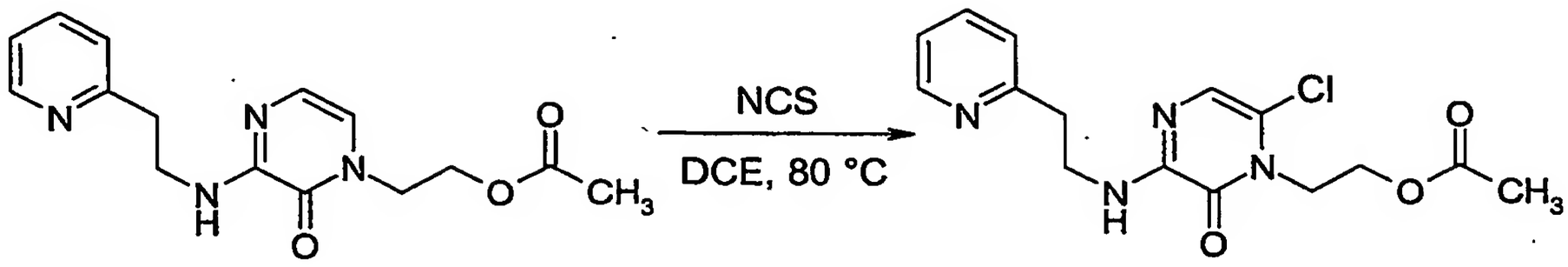


Acetic acid 2-[2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-ethyl ester.

A solution of 596 mg (2.29 mmol) of 1-(2-hydroxy-ethyl)-3-(2-pyridin-3-yl-ethylamino)-1*H*-pyrazin-2-one, 483 µL (3.43 mmol) of triethylamine and 14.0 mg (0.115 mmol) of 4-dimethylaminopyridine is stirred for 5 min before 259 µL (2.75 mmol) of acetic anhydride is added. After stirring for 1 h at room temperature, the crude product is washed sequentially with saturated aqueous sodium bicarbonate solution, water and brine. The organic layer is dried with sodium sulfate and the solvent is removed under reduced pressure to yield 692 mg (quant.) of the title product.

LC/MS (I) (5-95%, 10 min): 1.97, 303 (M+H).

Step 3

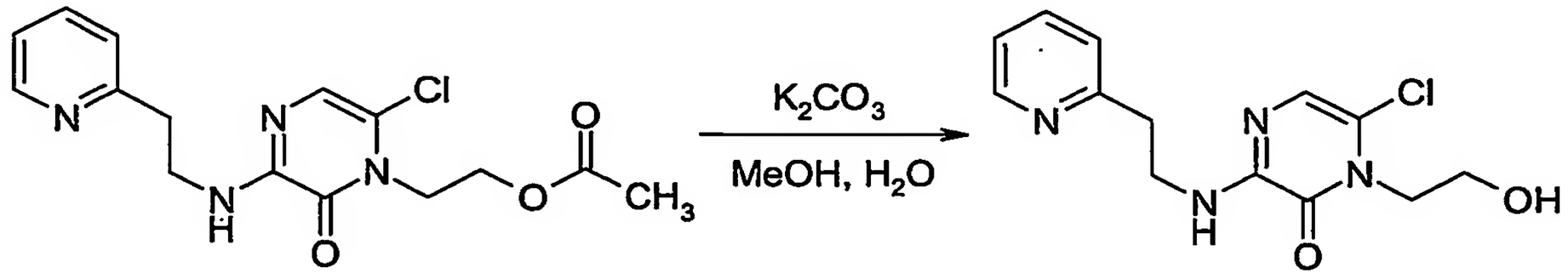


Acetic acid 2-[6-chloro-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-ethyl ester.

To 700 mg (2.31 mmol) of acetic acid 2-[2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-ethyl ester in 25 mL of 1,2-dichloroethane is added a solution of 309 mg (2.31 mmol) of *N*-chlorosuccinimide in 3 mL of 1,2-dichloroethane. The resulting mixture is heated for 90 min at 80 °C and then allowed to cool to room temperature before being washed sequentially with saturated aqueous sodium bicarbonate solution, water and brine. The organic layer is dried with sodium sulfate and the solvent is removed under reduced pressure. The crude product is purified by flash chromatography (silica gel, eluent: 20% to 100% ethyl acetate in cyclohexane) to yield 638 mg (82%) of the title compound.

LC/MS (I) (5-95%, 10 min): 2.36, 337 (M+H).

Step 4



6-Chloro-1-(2-hydroxy-ethyl)-3-(2-pyridin-2-yl-ethylamino)-1*H*-pyrazin-2-one.

To 76.0 mg (0.226 mmol) of acetic acid 2-[6-chloro-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-ethyl ester in 3 mL of methanol is added 1 mL of 1M potassium carbonate solution. The resulting mixture is stirred for 1 h at room temperature, then acidified with a 0.2N hydrochloric acid solution and washed once with dichloromethane. The aqueous phase is separated, neutralised with saturated aqueous sodium bicarbonate solution and extracted six times with dichloromethane. The organic phases

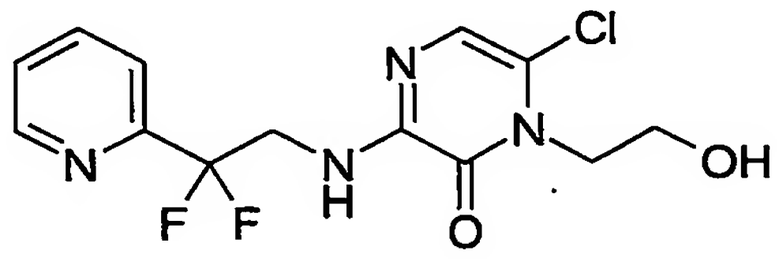
are collected, dried with sodium sulfate and the solvent is evaporated under reduced pressure to give 66.5 mg (quant.) of the title compound.

^{1}H-NMR (300 MHz) δ = 2.98-3.03 (m, 2H), 3.58-3.65 (m, 4H), 4.09-4.13 (m, 2H), 4.86 (bs, 1H), 6.81 (s, 1H), 7.21-7.29 (m, 3H), 7.63-7.68 (m, 1H), 8.44-8.45 (m, 1H).

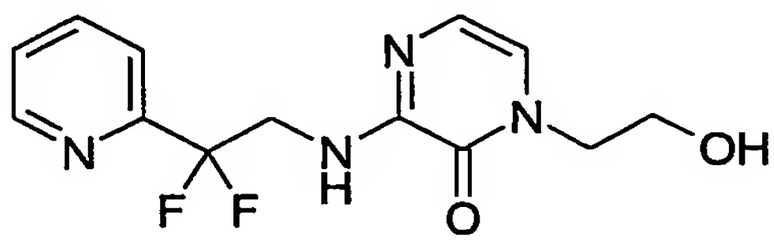
LC/MS (I) (5-95%, 10 min): 1.92, 295 (M+H).

Using a procedure similar to the one outlined above, the following compounds were prepared.

Example 15



Step 1

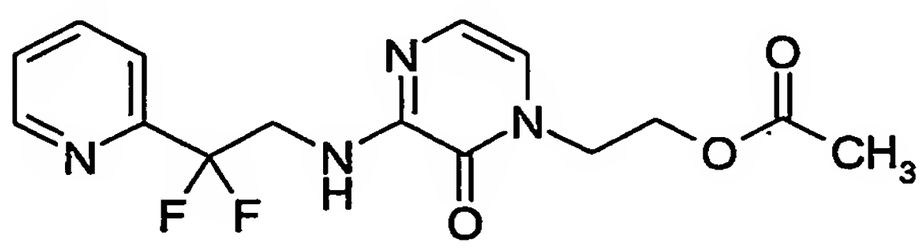


3-(2,2-Difluoro-2-pyridin-2-yl-ethylamino)-1-(2-hydroxy-ethyl)-1*H*-pyrazin-2-one.

Obtained from [3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-acetic acid ethyl ester.

LC/MS (I) (5-95%, 10 min): 3.25, 297 (M+H).

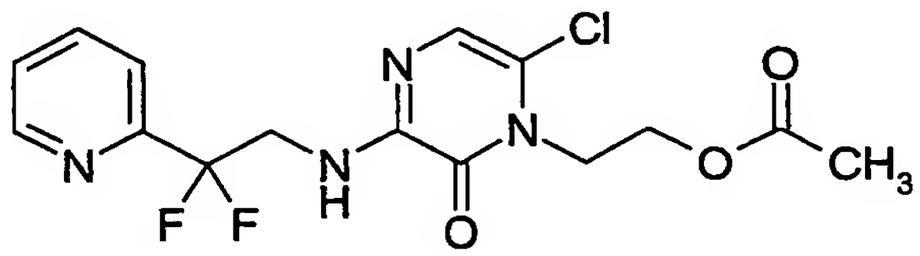
Step 2



Acetic acid 2-[3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-ethyl ester.

LC/MS (II) (5-95%, 10 min): 4.33, 339 (M+H).

Step 3

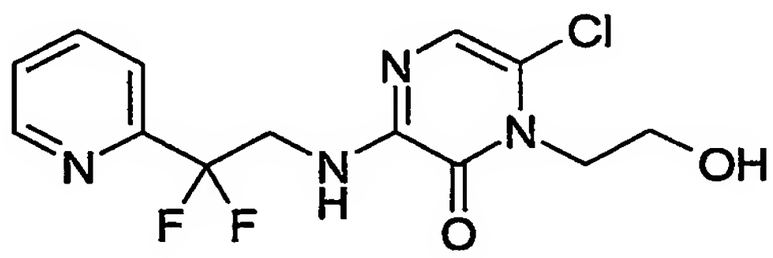


Acetic acid 2-[6-chloro-3-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-2-oxo-2*H*-pyrazin-1-yl]-ethyl ester (TFA salt).

^{1}H-NMR (300 MHz) δ = 1.95 (s, 3H), 4.15-4.30 (m, 6H), 6.88 (s, 1H), 7.26-7.30 (m, 1H), 7.50-7.54 (m, 1H), 7,63-7.66 (m, 1H), 7.91-7.96 (m, 1H), 8.63 (d, 1H).

LC/MS (II) (5-95%, 10 min): 3.72, 373 (M+H).

Step 4

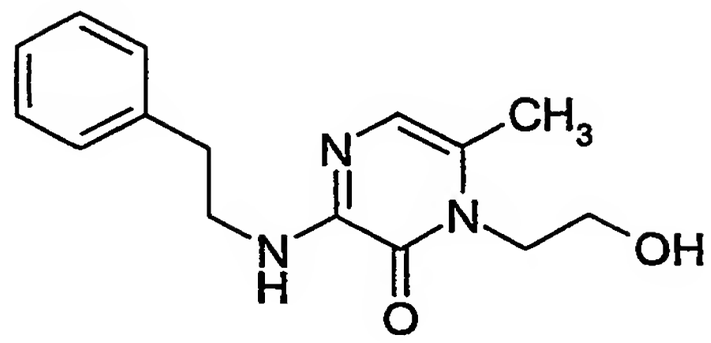


6-Chloro-2-(2,2-difluoro-2-pyridin-2-yl-ethylamino)-1-(2-hydroxy-ethyl)-1*H*-pyrazin-2-one.

^{1}H-NMR (300 MHz) δ = 3.57-3.63 (m, 2H), 3.78 (s, 2H), 4.10-4.27 (m, 2H), 4.86-4.90 (m, 1H), 6.68 (s, 1H), 7.18-7.22 (m, 1H), 7.50-7.54 (m, 1H), 7.64-7.67 (m, 1H), 7.91-7.96 (m, 1H), 8.66 (d, 1H).

LC/MS (I) (5-95%, 10 min): 3.25, 331 (M+H).

Example 16



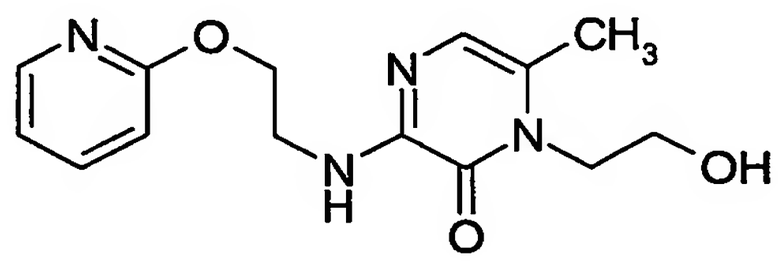
1-(2-Hydroxy-ethyl)-6-methyl-3-phenethylamino-1*H*-pyrazin-2-one.

Obtained from (6-methyl-2-oxo-3-phenethylamino-2*H*-pyrazin-1-yl)-acetic acid ethyl ester according to the procedure described for Step 1 in Example 14.

^{1}H-NMR (300 MHz) δ = 2.19 (s, 3H), 2.81-2.86 (m, 2H), 3.44-3.51 (m, 2H), 3.57-3.62 (m, 2H), 3.91-3.95 (m, 2H), 4.82-4.84 (t, 1H), 6.59 (s, 1H), 6.65-6.68 (m, 1H), 7.13-7.27 (s, 5H).

LC/MS (II) (5-95%, 10 min): 2.19, 274 (M+H).

Example 17

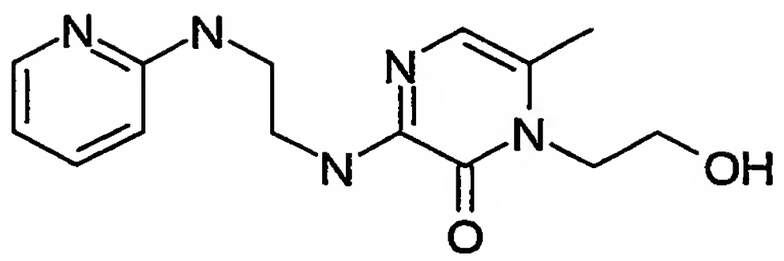


1-(2-Hydroxy-ethyl)-6-methyl-3-[2-(pyridin-2-yloxy)-ethylamino]-1*H*-pyrazin-2-one.

Obtained from {6-methyl-2-oxo-3-[2-(pyridin-2-yloxy)-ethylamino]-2H-pyrazin-1-yl}-acetic acid ethyl ester according to the procedure described for Step 1 in Example 14. The crude mixture was taken directly onto the next step.

LC/MS (I) (5-95%, 10 min): 1.30, 291 (M+H).

Example 18

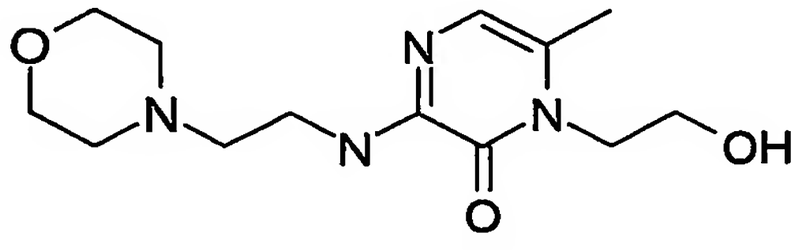


1-(2-Hydroxy-ethyl)-6-methyl-3-[2-(pyridin-2-ylamino)-ethylamino]-1*H*-pyrazin-2-one

Obtained from {6-Methyl-2-oxo-3-[2-(pyridin-2-ylamino)-ethylamino]-2H-pyrazin-1-yl}-acetic acid ethyl ester according to the procedure described for Step 1 in Example 14.

The crude mixture [LC/MS (I) (5-95%, 10 min): 1.94, 290 (M+H)] was taken directly onto the next step.

Example 19



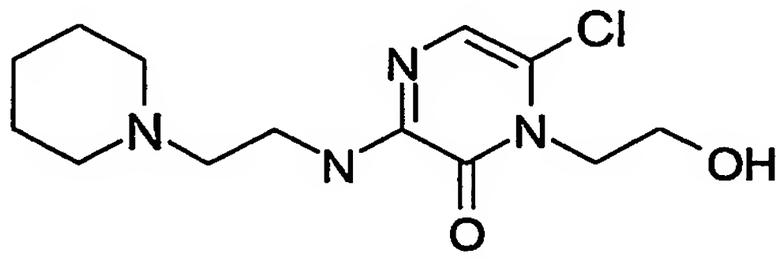
1-(2-Hydroxy-ethyl)-6-methyl-3-(2-morpholin-4-yl-ethylamino)-1H-pyrazin-2-one

Obtained from [6-Methyl-3-(2-morpholin-4-yl-ethylamino)-2-oxo-2H-pyrazin-1-yl]-acetic acid ethyl ester according to the procedure described for Step 1 in Example 14.

The crude mixture was taken directly onto the next step.

LC/MS (I) (5-90%, 5 min): 1.50, 283 (M+H).

Example 20

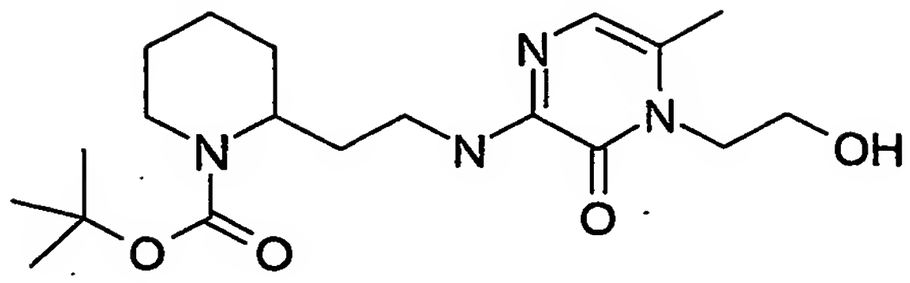


6-Chloro-1-(2-hydroxy-ethyl)-3-(2-piperidin-1-yl-ethylamino)-1H-pyrazin-2-one

Obtained from [2-Oxo-3-(2-piperidin-1-yl-ethylamino)-2H-pyrazin-1-yl]-acetic acid ethyl ester according to the procedure described in Example 14 (steps 1 to 4).

LC/MS (I) (5-90%, 5 min): 1.50, 283 (M+H).

Example 21



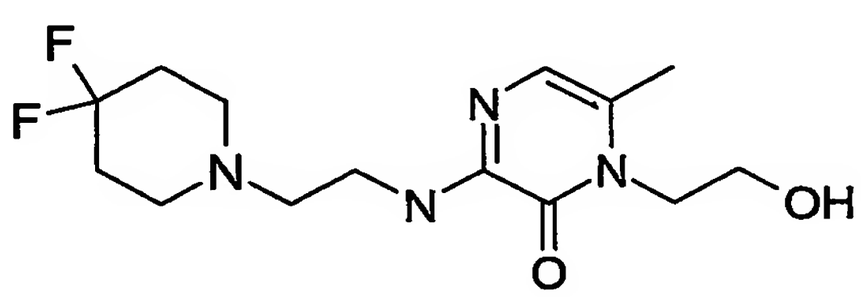
2-{2-[4-(2-Hydroxy-ethyl)-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

Obtained from 2-[2-(4-ethoxycarbonylmethyl-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester according to the procedure described for Step 1 in Example 14.

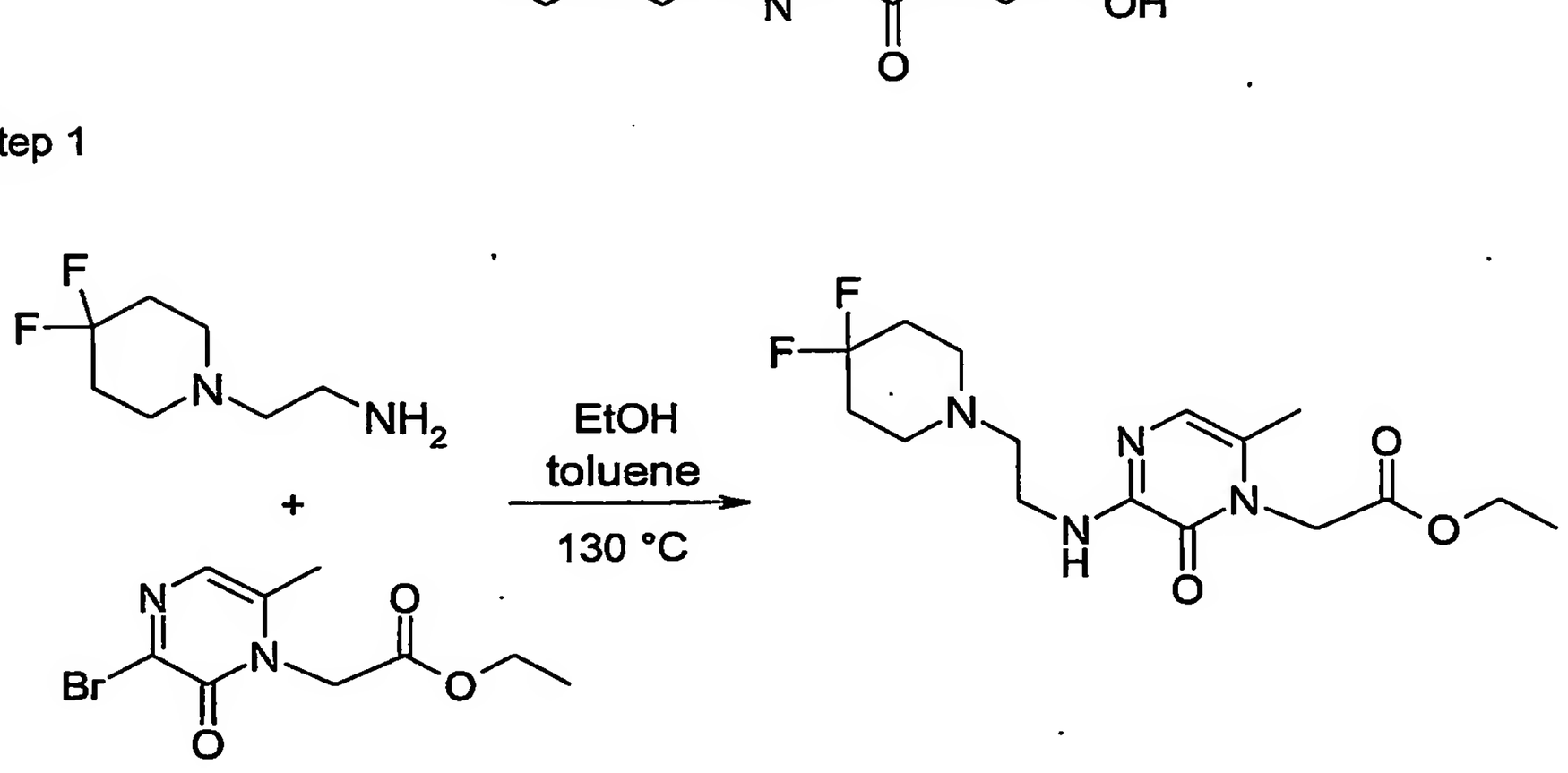
^{1}H-NMR (300 MHz) δ = 1.35 (s, 9H), 1.43- 1.70 (m, 6H), 1.85-1.98 (m, 1H), 2.18 (s, 3H), 2.71-2.80 (m, 1H), 3.00-3.20 (m, 1H), 3.56-3.62 (m, 1H), 3.75-3.85 (m, 1H), 3.90-3.94 (m, 2H), 4.10- 4.20 (m, 1H), 4.82-4.85 (m, 1H), 6.55 (s, 1H), 6.62-6.65 (m, 1H).

LC/MS (II) (5-95%, 5 min): 2.35, 381 (M+H).

Example 22



Step 1



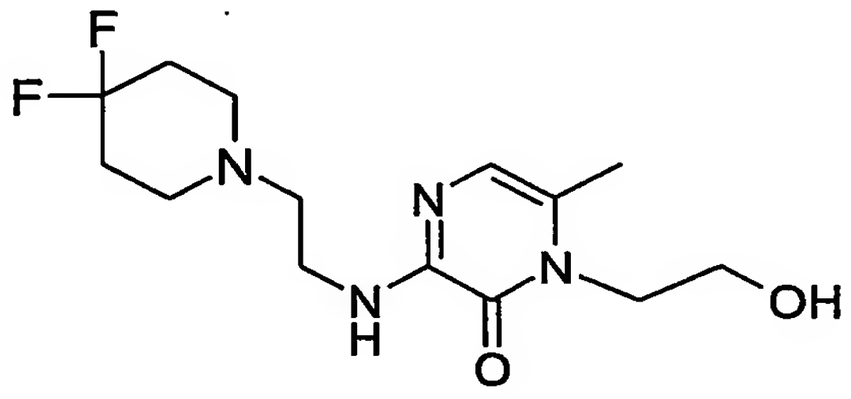
{3-[2-(4,4-Difluoro-piperidin-1-yl)-ethylamino]-6-methyl-2-oxo-2H-pyrazin-1-yl}-acetic acid ethyl ester

Obtained from (3-bromo-6-methyl-2-oxo-2H-pyrazin-1-yl)-acetic acid ethyl ester and 2-(4,4-difluoro-piperidin-1-yl)-ethylamine according to the procedure described in Example 13.

^{1}H-NMR (300 MHz) δ = 1.20 (t, 3H), 1.86-2.02 (m, 4H), 2.07 (s, 3H), 2.45-2.62 (m, 6H), 3.35 (q, 2H), 4.11-4.18 (q, 2H), 4.71 (s, 2H), 6.62 (s, 1H), 6.63-6.70 (m, 1H).

LC/MS (I) (5-95%, 5 min): 1.75, 359 (M+H)]

Step 2



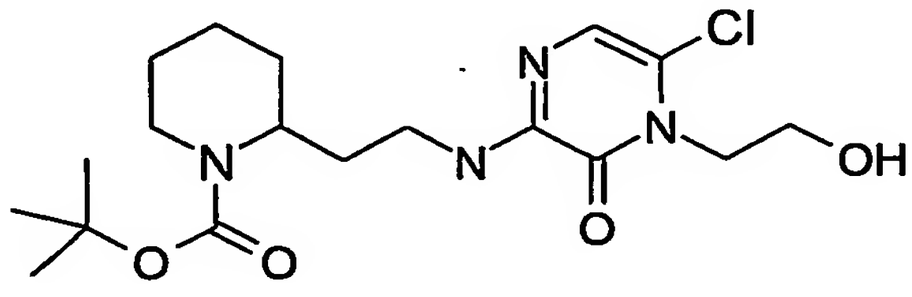
3-[2-(4,4-Difluoro-piperidin-1-yl)-ethylamino]-1-(2-hydroxy-ethyl)-6-methyl-1H-pyrazin-2-one

Obtained from {3-[2-(4,4-difluoro-piperidin-1-yl)-ethylamino]-6-methyl-2-oxo-2H-pyrazin-1-yl}-acetic acid ethyl ester according to the procedure described for Step 1 in Example 14.

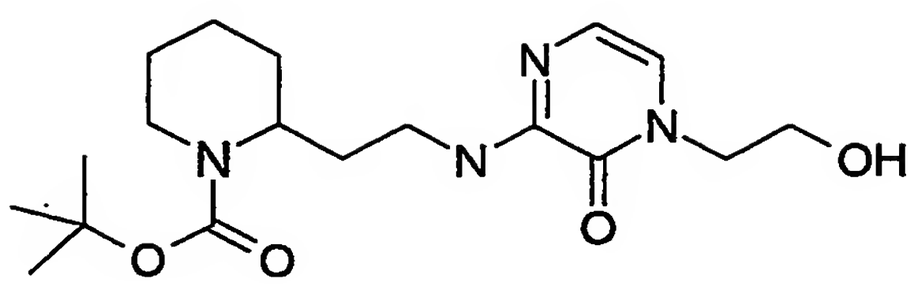
LC/MS (I) (5-95%, 5 min): 1.60, 317 (M+H).

Using a procedure similar to the one outlined in Example 14, the following compounds were prepared.

Example 23



Step 1

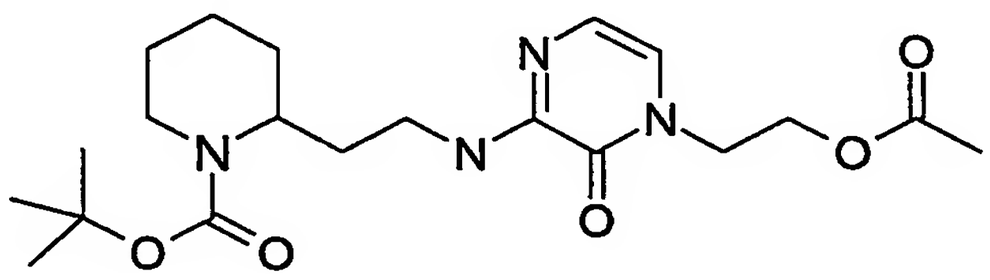


2-{2-[4-(2-Hydroxy-ethyl)-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

Obtained from 2-[2-(4-Ethoxycarbonylmethyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester.

LC/MS (I) (5-90%, 5 min): 2.23, 367 (M+H).

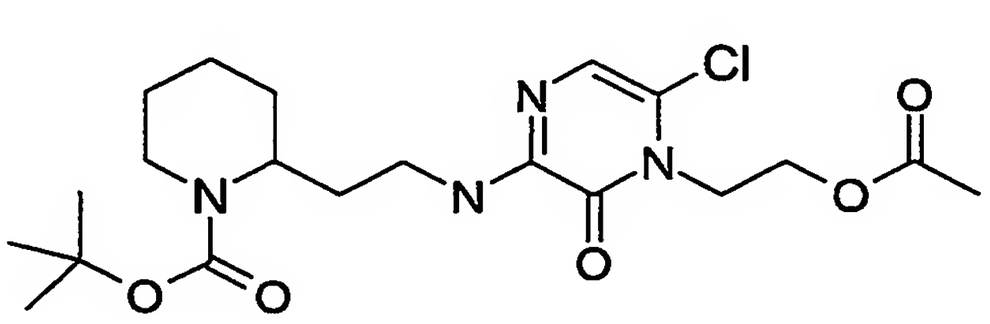
Step 2



2-{2-[4-(2-Acetoxy-ethyl)-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

LC/MS (I) (5-90%, 5 min): 2.50, 409 (M+H).

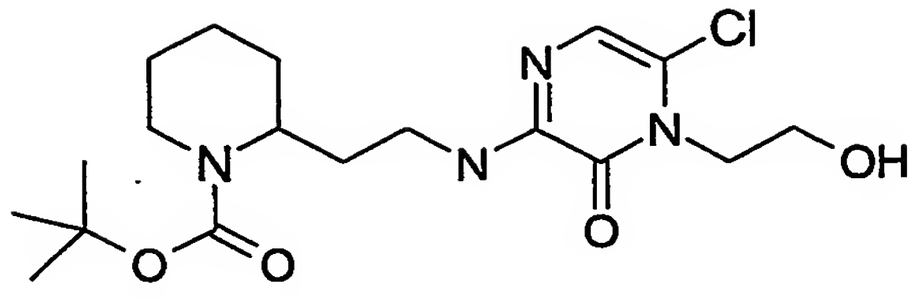
Step 3



2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

LC/MS (I) (5-90%, 5 min): 3.23, 443 (M+H).

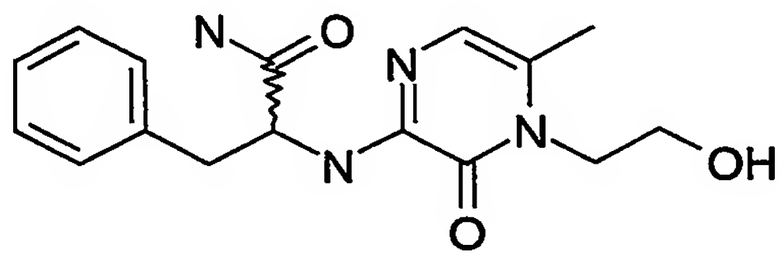
Step 4



2-{2-[5-Chloro-4-(2-hydroxy-ethyl)-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

LC/MS (I) (5-90%, 5 min): 2.61, 401 (M+H).

Example 24

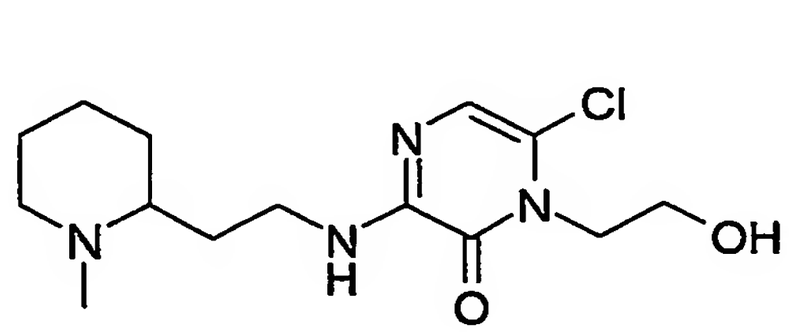


2-[4-(2-Hydroxy-ethyl)-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-3-phenyl-propionamide

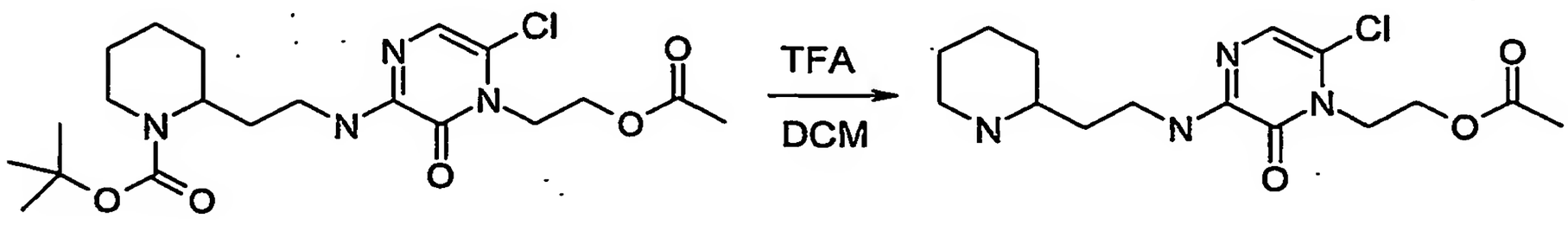
Obtained from [3-(1-Carbamoyl-2-phenyl-ethylamino)-6-methyl-2-oxo-2H-pyrazin-1-yl]-acetic acid ethyl ester according to the procedure described for Step 1 in Example 14. The crude mixture was taken directly onto the next step.

LC/MS (I) (5-90%, 5 min): 1.76, 317 (M+H).

Example 25



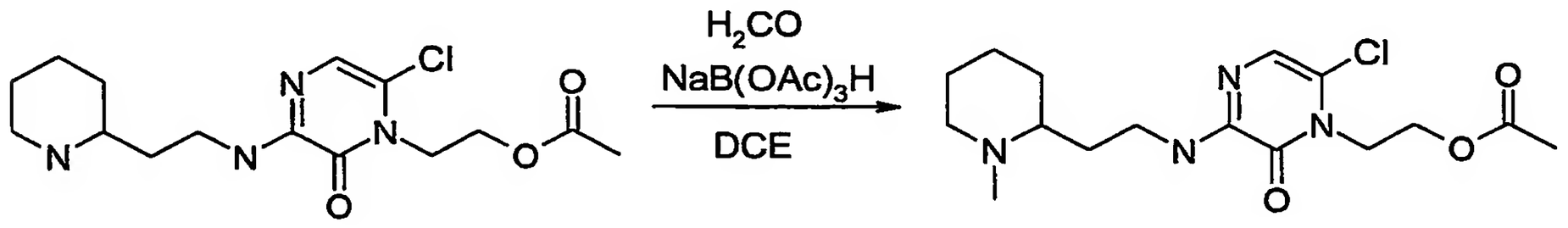
Step 1



Acetic acid 2-[6-chloro-2-oxo-3-(2-piperidin-2-yl-ethylamino)-2H-pyrazin-1-yl]-ethyl ester

2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester (282 mg, 0.637 mmol) is dissolved in 6 mL dichloromethane and 2 mL TFA is added. The solution is stirred 1 h at room temperature, 10 mL toluene are added and the solvent is evaporated under reduced pressure. The crude product is used in the next step without further purification.

Step 2

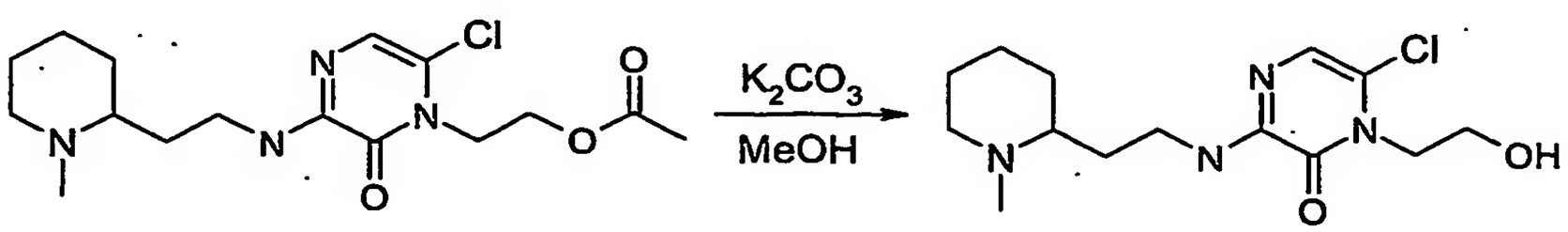


Acetic acid 2-{6-chloro-3-[2-(1-methyl-piperidin-2-yl)-ethylamino]-2-oxo-2H-pyrazin-1-yl}-ethyl ester

Acetic acid 2-[6-chloro-2-oxo-3-(2-piperidin-2-yl-ethylamino)-2H-pyrazin-1-yl]-ethyl ester (73.0 mg, 0.213 mmol) is dissolved in 2 mL dichloroethane under argon. 34,6 µL of a 37% solution of formaldehyde in water are added and then sodium triacetoxyborohydride (90.3 mg, 0.426 mmol) is added to the solution. The solution is stirred for 3 h, methanol (1 mL) is added and the solvents are evaporated under reduced pressure. The crude product was dissolved in DCM: water (6:1), the organic phase is washed with saturated solution of sodium bicarbonate, water and brine and dried over sodium sulfate. The solvent is evaporated under reduced pressure and the crude product is purified by column chromatography (silica gel, eluent = 10% methanol in DCM, with 0.5% NH_4OH).

LC/MS (I) (5-95%, 5 min): 1.78, 357 (M+H).

Step 3

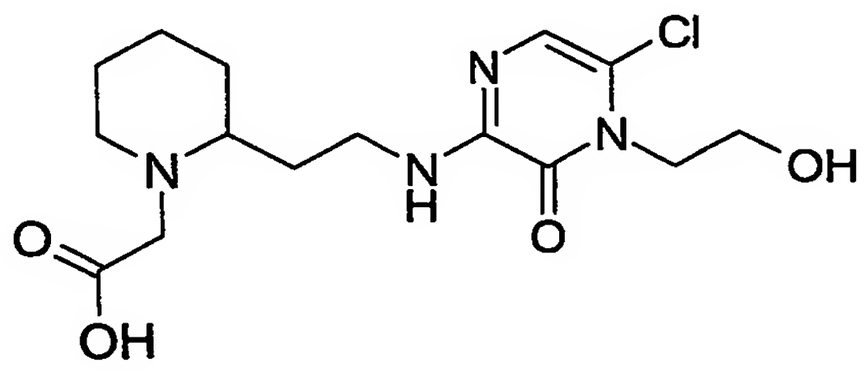


6-Chloro-1-(2-hydroxy-ethyl)-3-[2-(1-methyl-piperidin-2-yl)-ethylamino]-1H-pyrazin-2-one

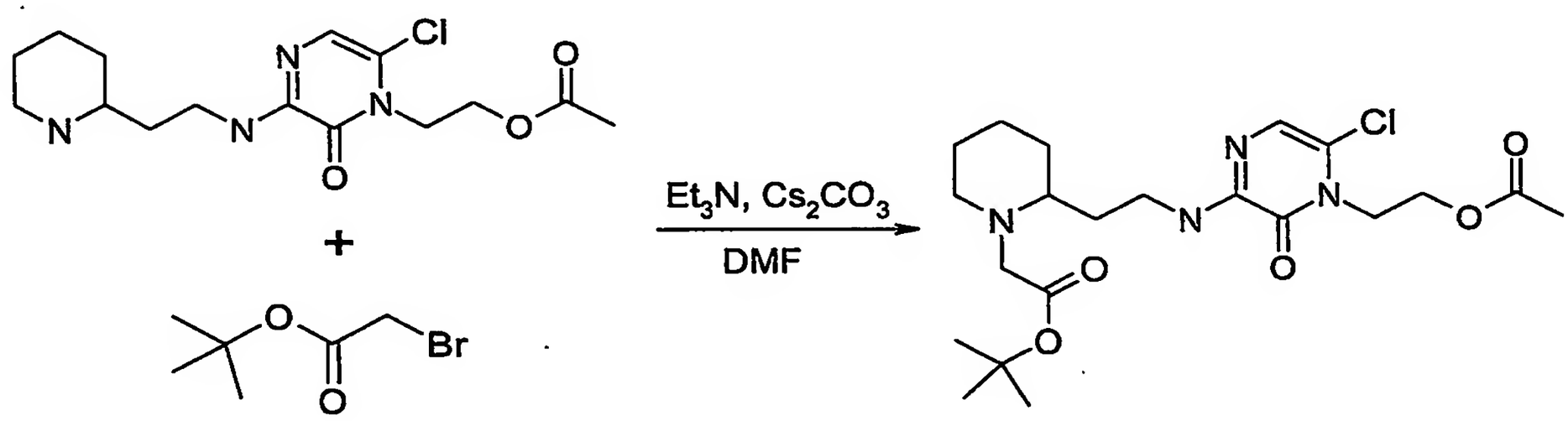
Obtained from acetic acid 2-{6-chloro-3-[2-(1-methyl-piperidin-2-yl)-ethylamino]-2-oxo-2H-pyrazin-1-yl}-ethyl ester according to the procedure described for Step 3 in Example 14.

LC/MS (I) (5-95%, 5 min): 1.60, 315 (M+H).

Example 26



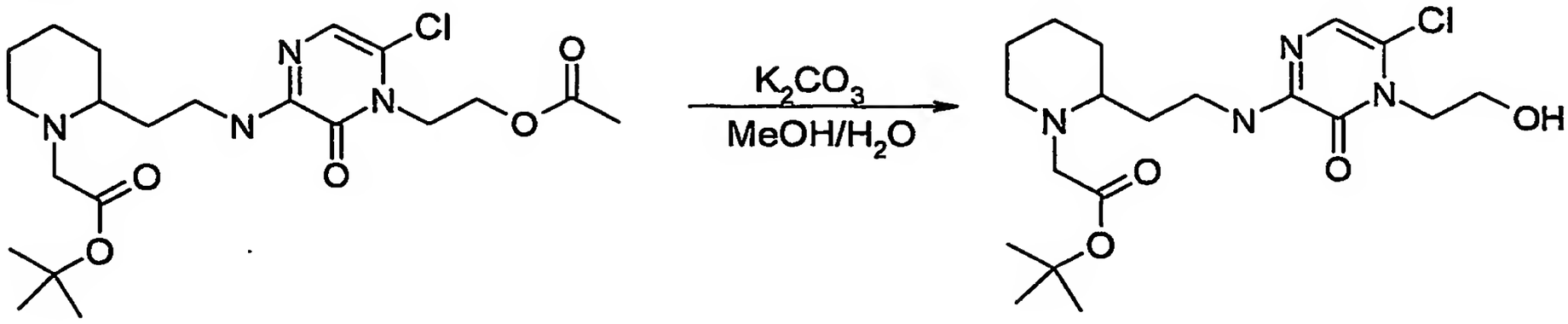
Step 1



(2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-iperidin-1-yl)-acetic acid tert-butyl ester

To a solution of acetic acid 2-[6-chloro-2-oxo-3-(2-piperidin-2-yl-ethylamino)-2H-pyrazin-1-yl]-ethyl ester (90 mg, 0.273 mmol) in 3 mL DMF, bromoacetic acid tertbutyl ester (46.7 mg, 0.237 mmol), triethylamine (99.2 µL, 0.712 mmol) and cesium carbonate (116 mg, 0.356 mmol) are added. The solution is stirred overnight, the solvent is evaporated and the crude product is dissolved in DCM, washed with saturated solution of sodium bicarbonate and dried over sodium sulfate. The crude product was purified by column chromatography (silica gel, eluent = 0% to 2% methanol in DCM) giving a yield of 68%.

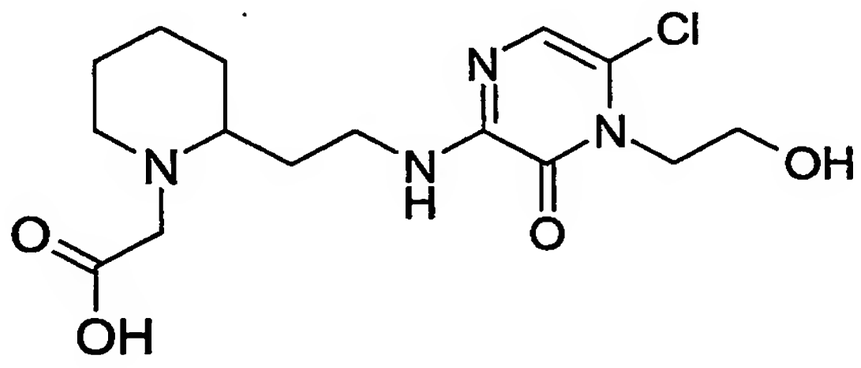
Step 2



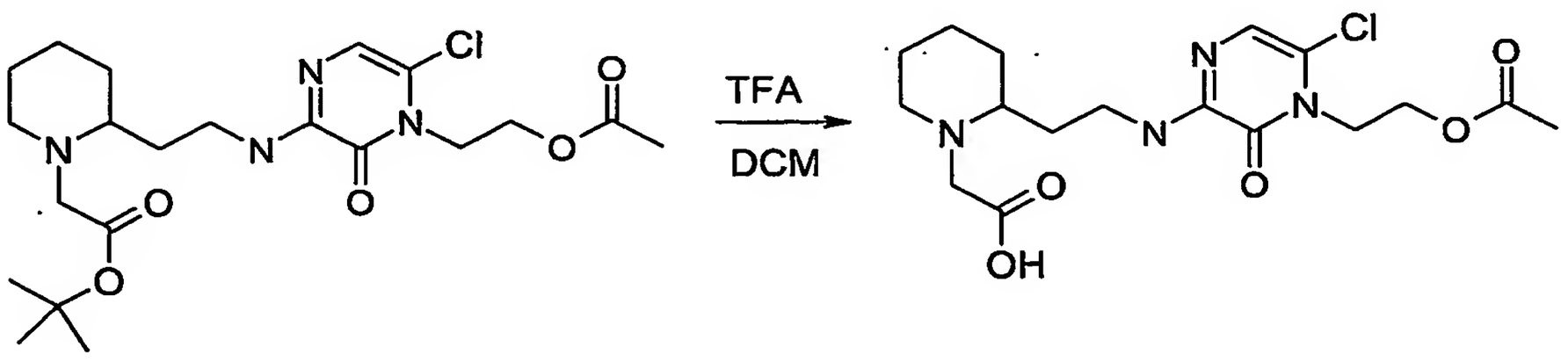
(2-{2-[5-Chloro-4-(2-hydroxy-ethyl)-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidin-1-yl)-acetic acid tert-butyl ester

Obtained from (2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-iperidin-1-yl)-acetic acid tert-butyl ester according to the procedure described for Step 3 in Example 14.

Example 27



Step 1

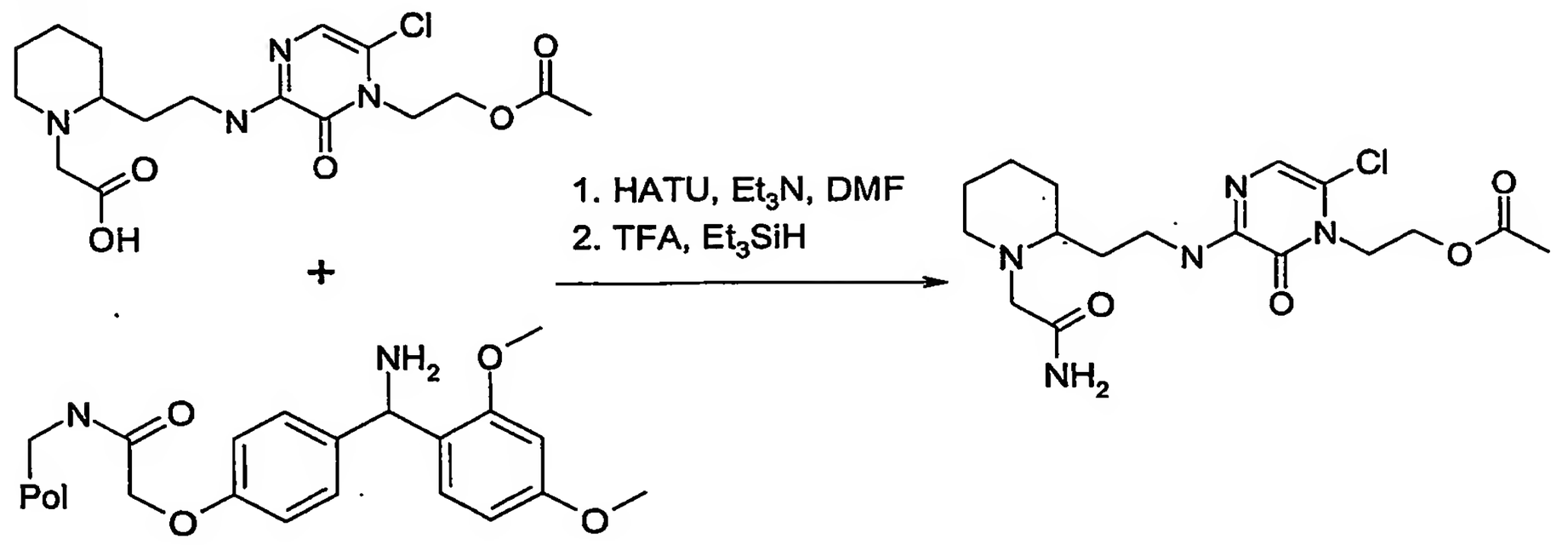


(2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidin-1-yl)-acetic acid

(2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidin-1-yl)-acetic acid tert-butyl ester (46 mg, 0.101 mmol) was dissolved in a 20% solution of TFA in DCM. The solution is stirred by room temperature overnight and the

solvent is evaporated under vacuum. The product is used in the next step without further purification.

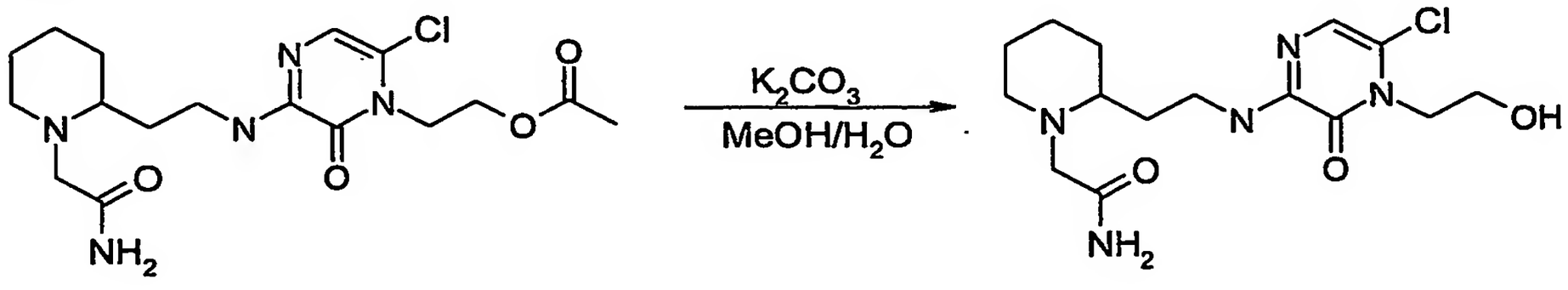
Step 2 and 3



Acetic acid 2-{3-[2-(1-carbamoylmethyl-piperidin-2-yl)-ethylamino]-6-chloro-2-oxo-2H-pyrazin-1-yl}-ethyl ester

Rink resin (0.86 mmol/g, 232 mg, 0.200 mmol) is shaken for 5 min in 5 mL DMF. The solvent is evaporated. (2-{2-[4-(2-Acetoxy-ethyl)-5-chloro-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidin-1-yl)-acetic acid (40.0 mg, 0.100 mmol), O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (37.9 mg,0.100 mmol) and Et_3N (55.6 µL, 0.399 mmol) are dissolved in 1.5 mL DMF and after 3 min the solution is added to the resin. The resin is shaked overnight and the solvent is removed.
To the resin 2 mL TFA/triethyl silane (95:5) are added and the resin is shaken by room temperature, yielding 24 mg product.

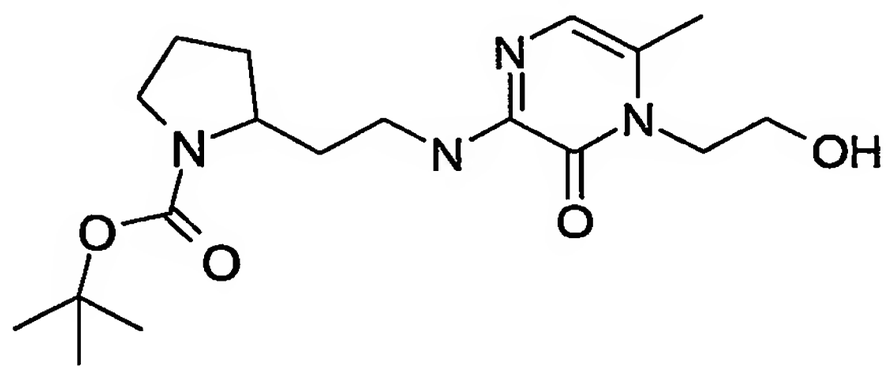
Step 4



2-(2-{2-[5-Chloro-4-(2-hydroxy-ethyl)-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidin-1-yl)-acetamide

Obtained from acetic acid 2-{3-[2-(1-carbamoylmethyl-piperidin-2-yl)-ethylamino]-6-chloro-2-oxo-2H-pyrazin-1-yl}-ethyl ester according to the procedure described for Step 3 in Example 14.

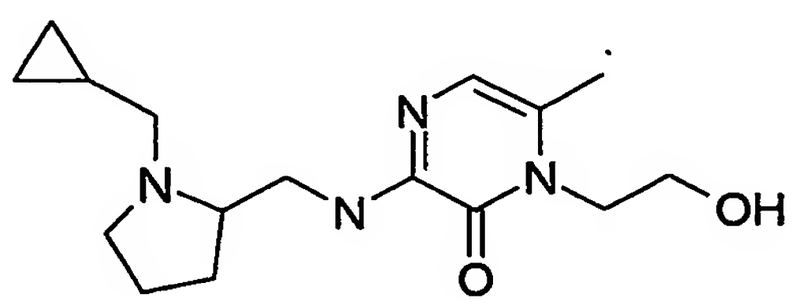
Example 28



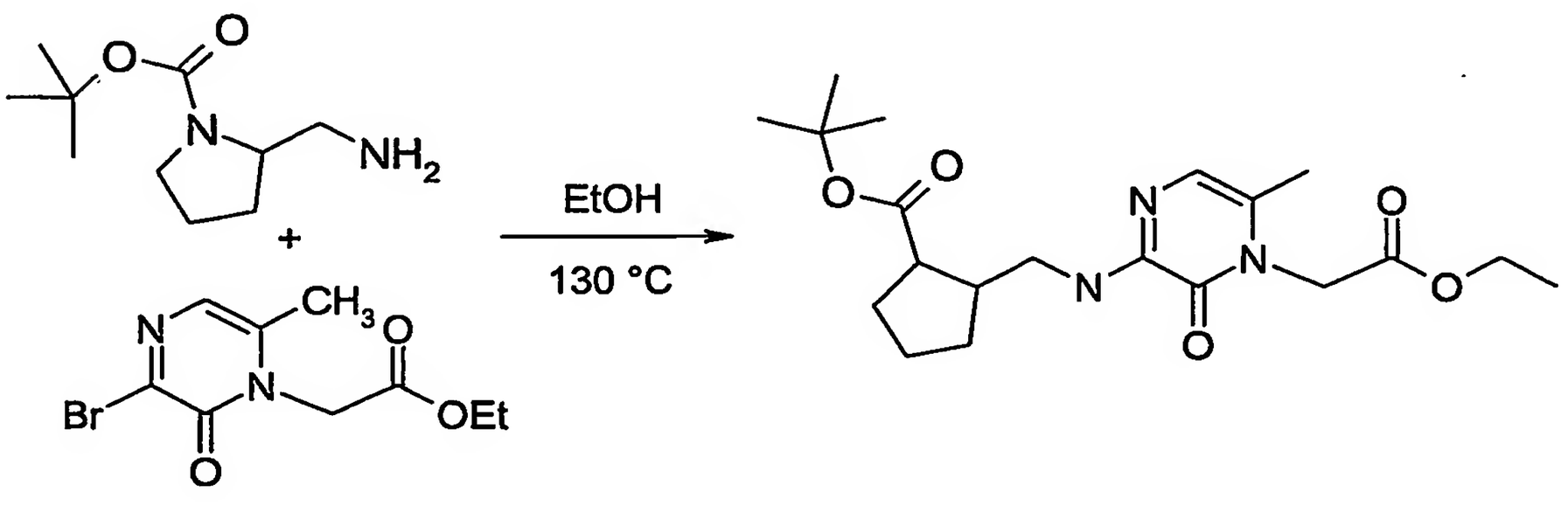
2-{2-[4-(2-Hydroxy-ethyl)-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-pyrrolidine-1-carboxylic acid tert-butyl ester

Obtained from 2-[2-(4-Ethoxycarbonylmethyl-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester according to the procedure described for Step 1 in Example 14.

Example 29



Step 1

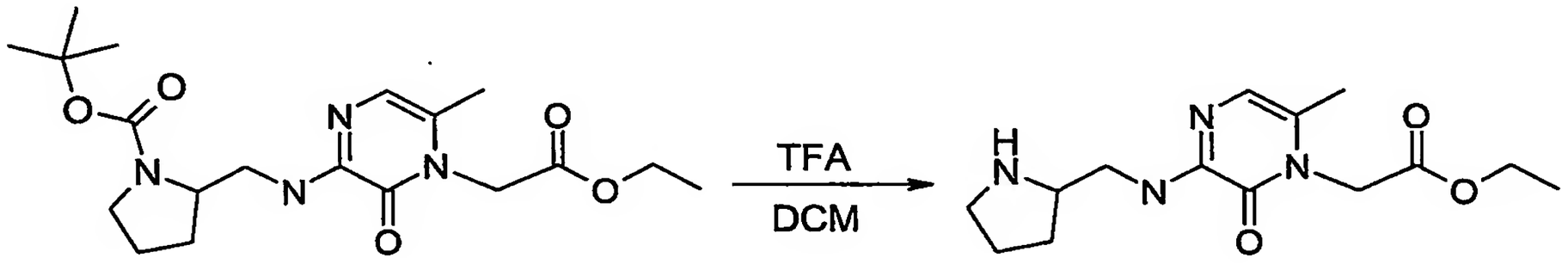


2-[2-(4-Ethoxycarbonylmethyl-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester

This compound is prepared using a procedure similar to the one outlined in Example 13.

LC/MS (I) (5-95%, 5 min): 2.20, 395 (M+2H).

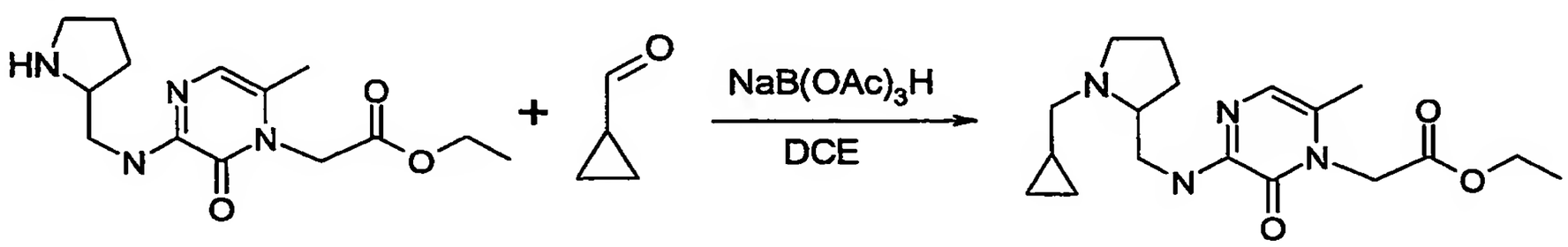
Step 2



[6-Methyl-2-oxo-3-(2-pyrrolidin-2-yl-ethylamino)-2H-pyrazin-1-yl]-acetic acid ethyl ester

2-[2-(4-Ethoxycarbonylmethyl-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-pyrrolidine-1-carboxylic acid tert-butyl ester (405 mg, 1.03 mmol) is dissolved in 5 mL dichloromethane and 2 mL TFA is added. The solution is stirred 3 h at room temperature and the solvent is evaporated under reduced pressure. The crude product is dissolved in methanol and the solvent is evaporated to give an orange solid, which is used in the next step without further purification.

Step 3

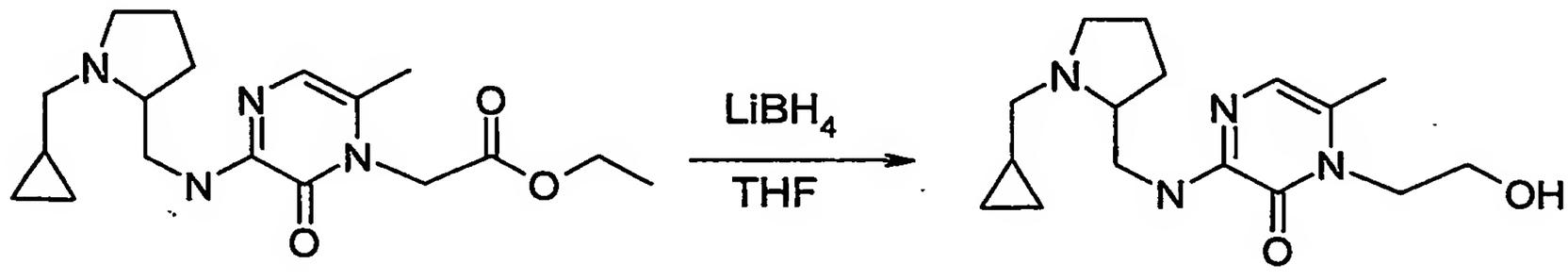


{3-[2-(1-Cyclopropylmethyl-pyrrolidin-2-yl)-ethylamino]-6-methyl-2-oxo-2H-pyrazin-1-yl}-acetic acid ethyl ester

To a solution of [6-methyl-2-oxo-3-(2-pyrrolidin-2-yl-ethylamino)-2H-pyrazin-1-yl]-acetic acid ethyl ester (100 mg, 0.199 mmol), cyclopropanecarbaldehyde (34.9 mg, 0.498 mmol) and triethylamine (69.4 µL, 0.498 mmol) in dichloroethane (5 mL) sodium triacetoxyborohydride (105 mg, 0.498 mmol) is added. The solution is stirred at room temperature for 3 h, diluted with DCM (5 mL) and the organic phase is washed with a saturated solution of sodium bicarbonate, water and brine, and dried over sodium sulfate. The solvent is evaporated under reduced pressure and the crude product was

purified by column chromatography chromatography (silica gel, eluent = 5% MeOH in DCM, with 0.5% NH_4OH) to give the pure product in 58 % yield.

Step 4

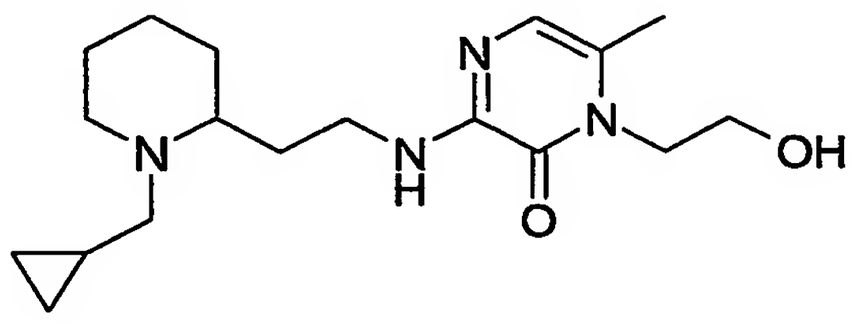


3-[2-(1-Cyclopropylmethyl-pyrrolidin-2-yl)-ethylamino]-1-(2-hydroxy-ethyl)-6-methyl-1H-pyrazin-2-one

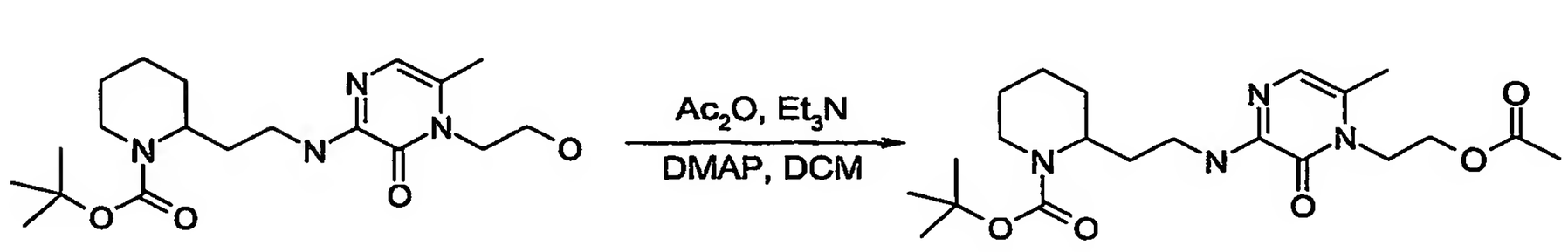
This compound is prepared using a procedure similar to the one outlined in step 1 of Examole 13.

LC/MS (I) (5-95%, 5 min): 1.63, 307 (M+H).

Example 30



Step 1

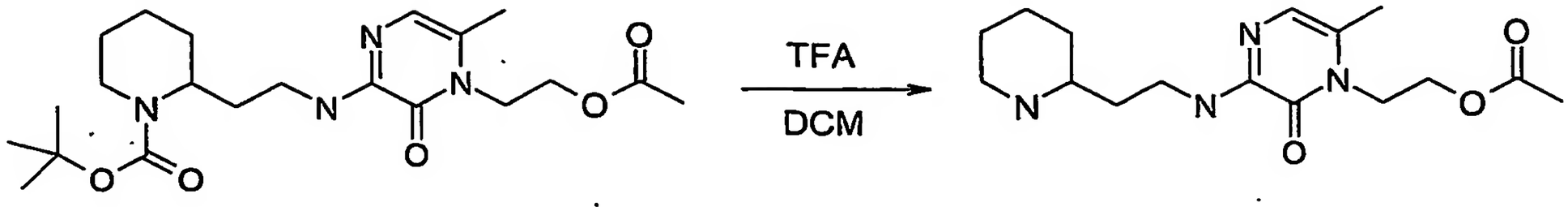


2-{2-[4-(2-Acetoxy-ethyl)-5-methyl-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester

This compound is prepared using a procedure similar to the one outlined in step 2 of Example 14.

LC/MS (I) (5-95%, 5 min): 1.63, 307 (M+H).

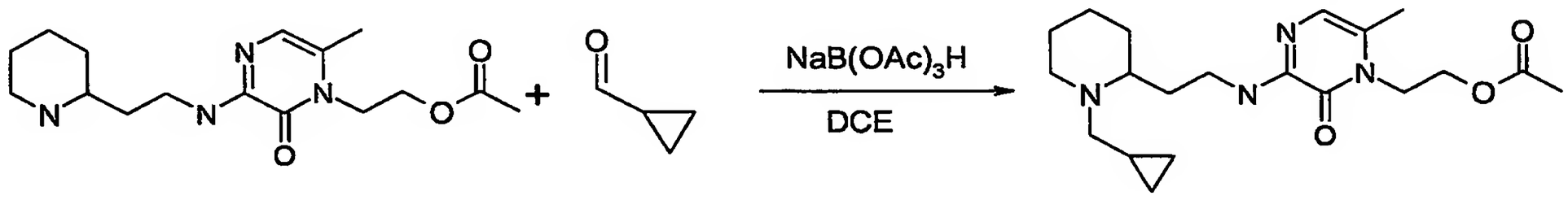
Step 2



Acetic acid 2-[6-methyl-2-oxo-3-(2-piperidin-2-yl-ethylamino)-2H-pyrazin-1-yl]-ethyl ester

This compound is prepared using a procedure similar to the one outlined in step 2 of Example 29.

Step 3

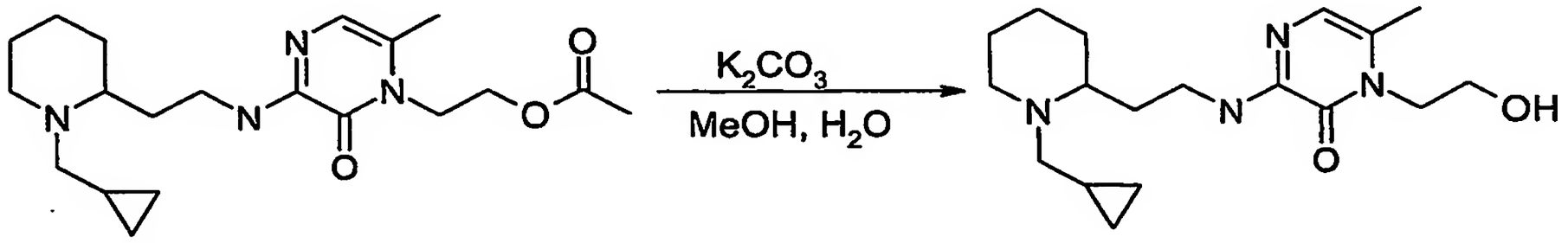


Acetic acid 2-{3-[2-(1-cyclopropylmethyl-piperidin-2-yl)-ethylamino]-6-methyl-2-oxo-2H-pyrazin-1-yl}-ethyl ester

This compound is prepared using a procedure similar to the one outlined in step 3 of Example 29.

LC/MS (I) (5-95%, 5 min): 1.28, 377 (M+H).

Step 4

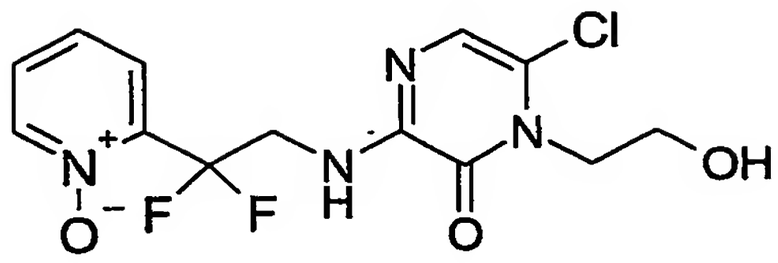


3-[2-(1-Cyclopropylmethyl-piperidin-2-yl)-ethylamino]-1-(2-hydroxy-ethyl)-6-methyl-1H-pyrazin-2-one

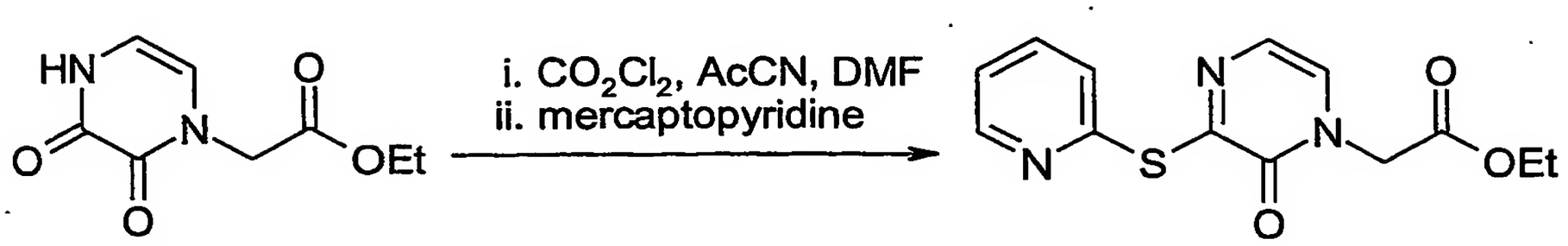
This compound is prepared using a procedure similar to the one outlined in step 4 of Example 14.

LC/MS (I) (5-95%, 5 min): 1.58, 335 (M+H).

Example 31



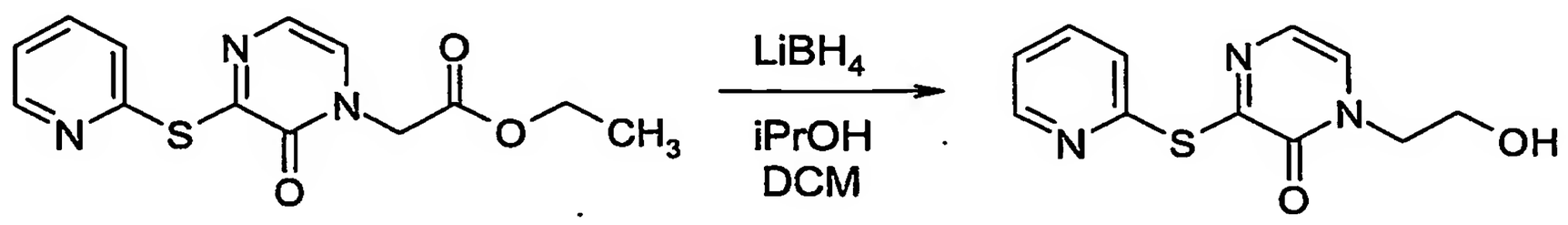
Step 1



[2-Oxo-3-(pyridin-2-ylsulfanyl)-2H-pyrazin-1-yl]-acetic acid ethyl ester

In a round-bottom flask equipped with nitrogen inlet, pyrazinone (2.00 g, 10.1 mmol) is dissolved in acetonitrile (14.0 mL) and DMF (0.20 mL). Oxalyl chloride (978 µL, 11.1 mmol) is added to the slurry mixture over 15 min at 20-25 °C. To the resulting yellow solution 2-mercaptopyridine (1.23 g, 11.1 mmol) is added in three equal portions at 20-min intervals. The mixture is stirred overnight at 82 °C. The solvent is evaporated and the crude product is redissolved in dichloromethane. The organic phase is washed with saturated sodium bicarbonate solution and water, dried over sodium sulfate and evaporated under reduced pressure. Purification by column chromatography (silica gel; eluent = 0% to 80% EtOAC in cyclohexane) gives 2.54 g (86%) of the product.
LC/MS (I) (5-95%, 5 min): 2.01, 292 (M+H).

Step 2



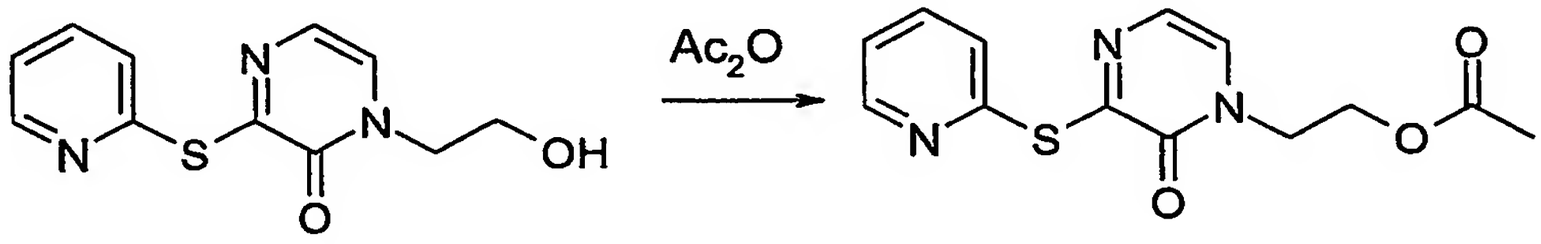
1-(2-Hydroxy-ethyl)-3-(pyridin-2-ylsulfanyl)-1H-pyrazin-2-one

To a solution of 800 mg (2.75 mmol) of [2-Oxo-3-(pyridin-2-ylsulfanyl)-2H-pyrazin-1-yl]-acetic acid ethyl ester in 8 mL of DCM and 4 mL isopropanol is added 1.10 mL (2.20 mmol) of a 2M lithium borohydride solution in tetrahydrofuran and the resulting

mixture is stirred overnight at –5 °C. After addition of 20 mL of methanol the mixture is stirred until gas evolution has ceased. The solvent is evaporated under reduced pressure and after column chromatography (silica gel; eluent = 0% to 2% methanol in DCM) the title product is isolated in quantitative yield.

LC/MS (I) (5-95%, 5 min): 1.61, 250 (M+H).

Step 3



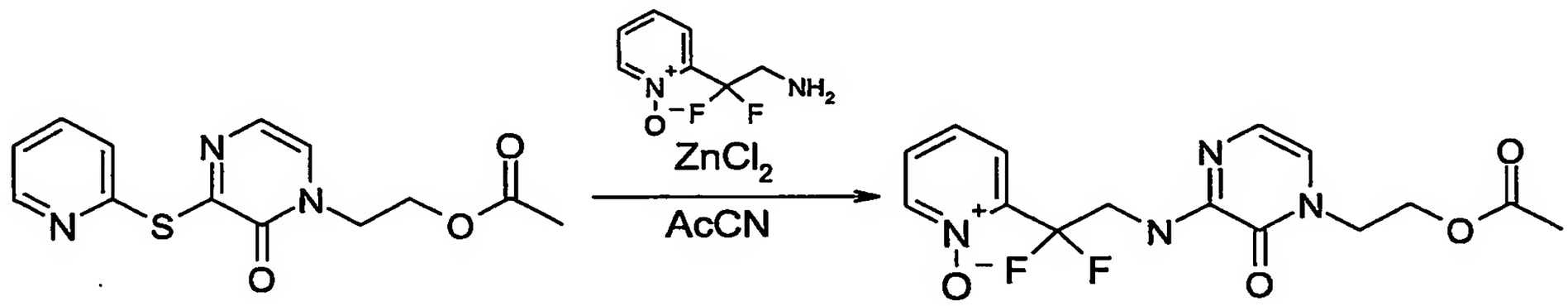
Acetic acid 2-[2-oxo-3-(pyridin-2-ylsulfanyl)-2H-pyrazin-1-yl]-ethyl ester

Obtained from 1-(2-Hydroxy-ethyl)-3-(pyridin-2-ylsulfanyl)-1H-pyrazin-2-one according to the procedure described for Step 2 in Example 14.

^{1}H-NMR (200 MHz) δ = 1.98 (s, 3H), 4.13-4.20 (m, 2H), 4.31-4.38 (m, 2H), 7.11-7.16 (d, 1H), 7.36-7.43 (m, 1H), 7.48-7.51 (d, 1H), 7.72-7.90 (m, 2H), 8.54-8.63 (m, 1H).

LC/MS (I) (5-95%, 5 min): 1.56, 292 (M+H).

Step 4

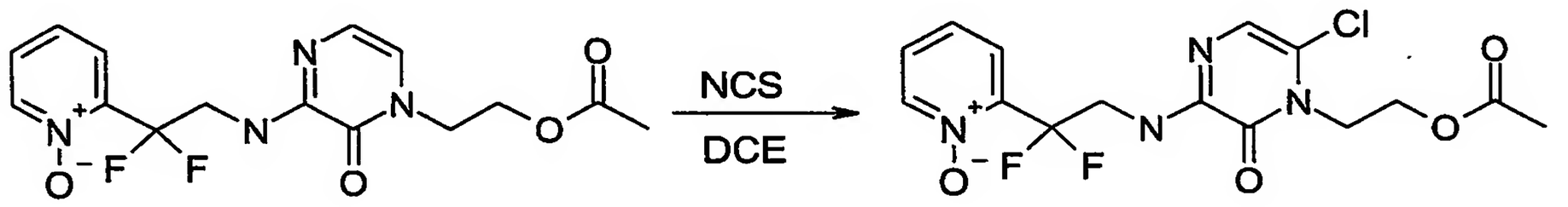


Acetic acid 2-{3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-2-oxo-2H-pyrazin-1-yl}-ethyl ester

2,2-Difluoro-2-(1-oxy-pyridin-2-yl)-ethylamine (269 mg, 1.54 mmol) and acetic acid 2-[2-oxo-3-(pyridin-2-ylsulfanyl)-2H-pyrazin-1-yl]-ethyl ester (375 mg, 1.29 mmol) are dissolved in acetonitrile in a sealed tube. Then zinc chloride (132 mg, 0.970 mmol) is added and the solution is heated to reflux at 82-84 °C under a N_2 atmosphere for 48 h. The reaction mixture is cooled to 22 °C, the solvent is evaporated and the crude mixture is purified by HPLC (446 mg, 1.25 mmol, 82% yield).

LC/MS (I) (5-95%, 5 min): 1.74, 355 (M+H).

Step 5

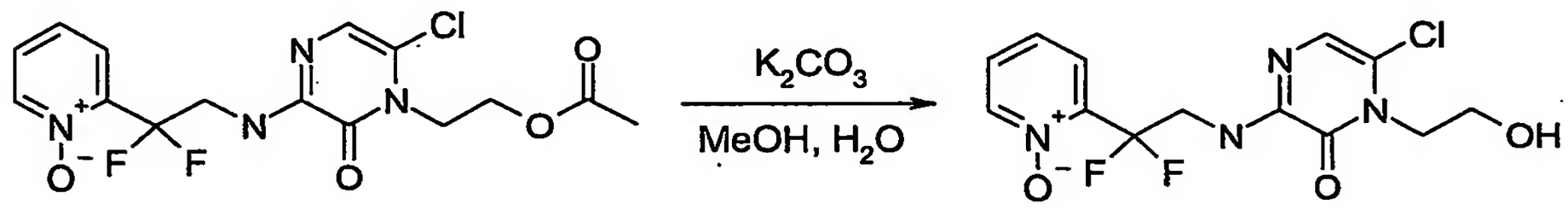


Acetic acid 2-{6-chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-2-oxo-2H-pyrazin-1-yl}-ethyl ester

Obtained from acetic acid 2-{3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-2-oxo-2H-pyrazin-1-yl}-ethyl ester according to the procedure described for Step 3 in Example 14. In this case the reaction was performed at 50 °C and the purification was performed by HPLC chromatography.

LC/MS (I) (5-95%, 5 min): 2.00, 389 (M+H).

Step 6



6-Chloro-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-1-(2-hydroxy-ethyl)-1H-pyrazin-2-one

Obtained from 1-(2-Hydroxy-ethyl)-3-(pyridin-2-ylsulfanyl)-1H-pyrazin-2-one according to the procedure described for Step 4 in Example 14.

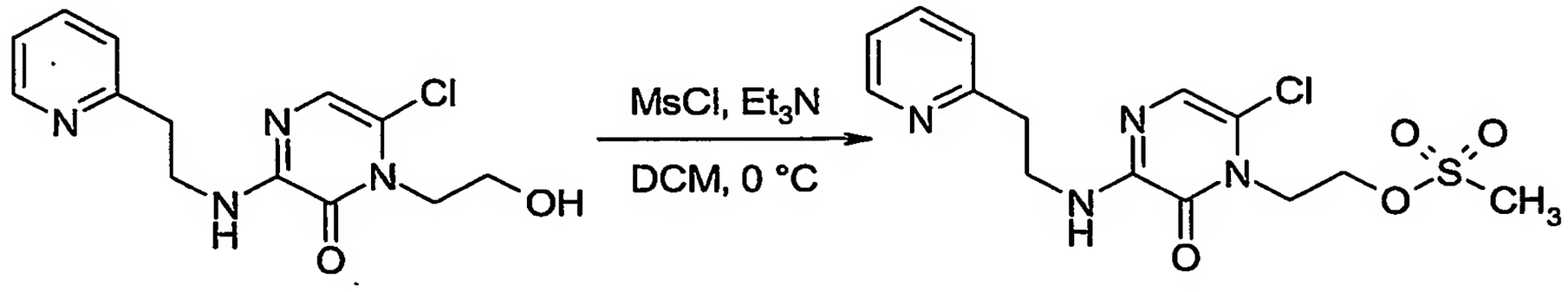
LC/MS (I) (5-95%, 5 min): 1.94, 347 (M+H).

The following examples deal with compounds of the invention synthesised according to Scheme O.

A description of the general procedure used for Step 1 follows.

Example 32

Step 1



Methanesulfonic acid 2-[6-chloro-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1yl]-ethyl ester.

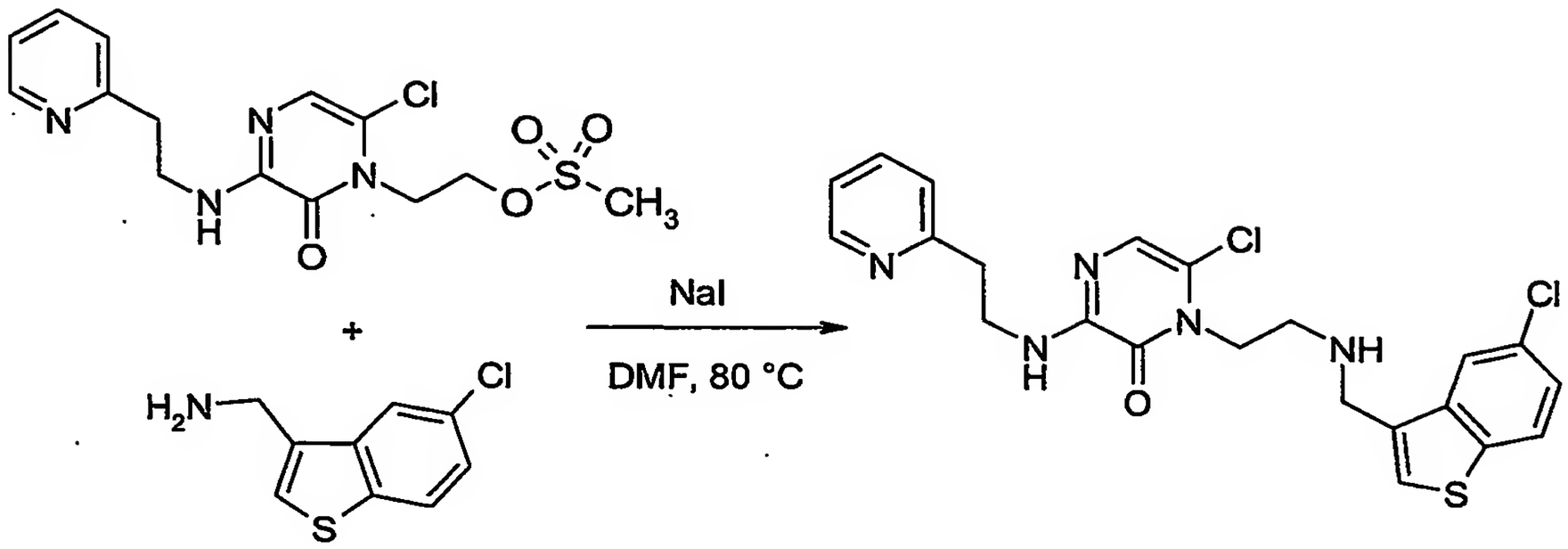
After addition of 83.5 µL(0.594 mmol) of triethylamine to a solution of 25.0 mg (0.085 mmol) of 6-chloro-1-(2-hydroxy-ethyl)-3-(2-pyridin-2-yl-ethylamino)-1*H*-pyrazin-2-one in 1 mL of dichloromethane, the reaction mixture is cooled to 0 °C with an ice bath and a solution of 14.4 µL (0.187 mmol) of methanesulfonylchloride in 1 mL of dichloromethane is added. The resulting solution is stirred for 30 min and then diluted with 5 mL of dichloromethane and washed with saturated aqueous sodium bicarbonate solution and brine. The organic layer is dried with sodium sulfate and concentrated under reduced pressure. The crude product is used without further purification.

LC/MS (I) (5-95%, 10 min): 2.85, 373 (M+H).

For Step 2 in Scheme O, Methods A through C may be used.

Step 2 : Method A

Example 33



6-Chloro-1-{2-[(5-chloro-benzo[b]thiophen-3-ylmethyl)amino]-ethyl}-3-(2-pyridin-2-yl-ethylamino)-1*H*-pyrazin-2-one.

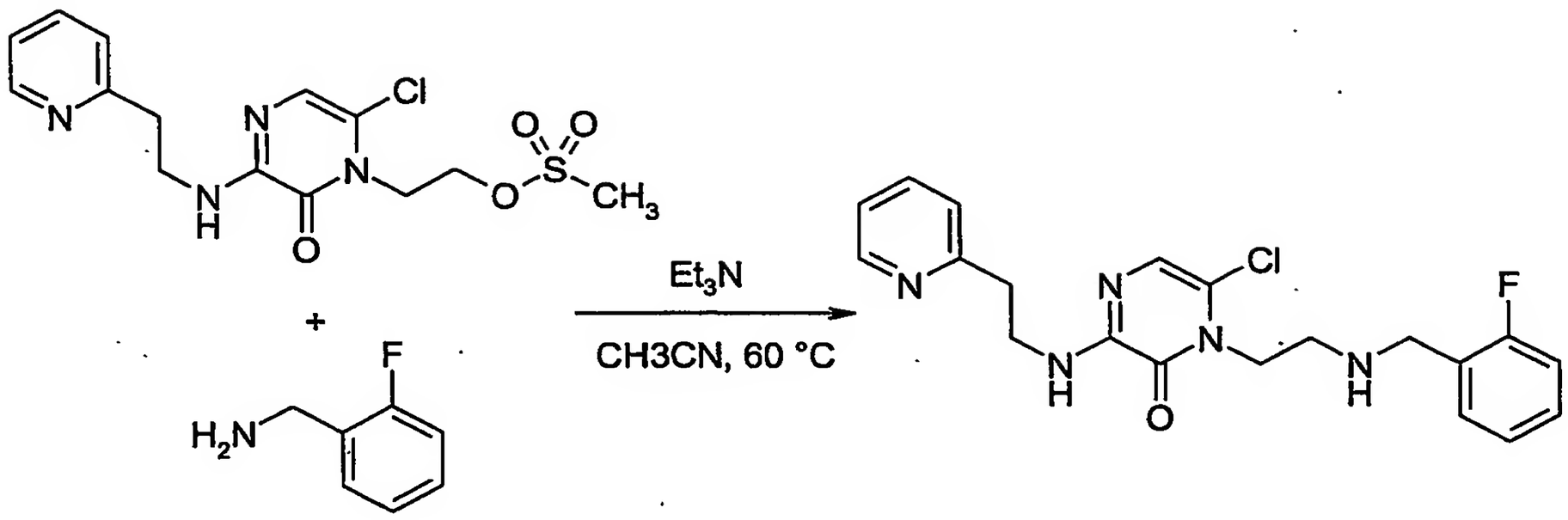
To a solution of 58.7 mg (0.157 mmol) of methanesulfonic acid 2-[6-chloro-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-ethyl ester and 23.6 mg (0.157 mmol) of sodium iodide in 6 mL of *N,N*-dimethylformamide is added 68.5 mg (0.346 mmol) of C-(5-chloro-benzo[b]thiophen-3-yl)methylamine. The mixture is stirred 3 h at 50 °C and additionally 10 h at 80 °C. The solution is then allowed to cool to room temperature and then washed sequentially with brine and water. The aqueous phases are extracted with ethyl acetate and dichloromethane. Organic layers are collected, washed with water, dried with sodium sulfate and the solvents are removed under vacuum. The crude product is purified by flash chromatography (silica gel, eluent: 0% to 2% methanol in dichloromethane) to yield 36.6 mg (49%) of the title compound.

^{1}H-NMR (200 MHz) δ = 2.82-2.87 (m, 2H), 2.97-3.02 (m, 2H), 3.58-3.64 (m, 2H), 3.95 (s, 2H), 4.12-4.17 (m, 2H), 6.85 (s, 1H), 7.15-7.23 (m, 3H), 7.32-7.35 (m, 1H), 7.55 (s, 1H), 7.62-7.67 (m, 1H), 7.89-7.95 (m, 2H), 8.44-8.45 (m, 1H).

LC/MS (I) (5-95%, 10 min): 2.92, 474 (M+H).

Step 2 : Method B

Example 34



6-Chloro-1-[2-(2-fluoro-benzylamino)-ethyl]-3-(2-pyridin-2-yl-ethylamino)-1*H*-pyrazin-2-one.

To a solution of 33.6 mg (0.090 mmol) of methanesulfonic acid 2-[6-chloro-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1-yl]-ethyl ester in 3 mL of acetonitrile is added 25.0 µL (0.180 mmol) of triethylamine and 13.0 µL (0.110 µmol) of 2-fluorobenzylamine. The mixture is stirred overnight at 60 °C and diluted with ethyl acetate (3 mL). The organic phase is washed sequentially with water, brine and water, dried with natrium sulfate and the solvent is removed under vacuum. Purification by column chromatography (silica gel, eluent: 2% to 10% methanol in dichloromethane) affords 10.9 mg (30%) of the title compound.

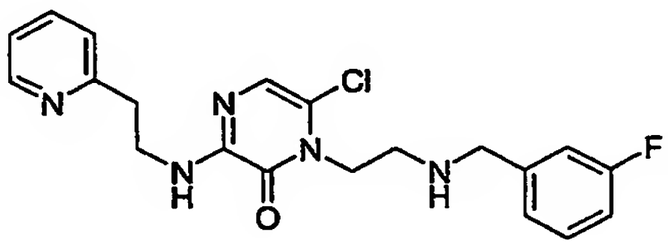
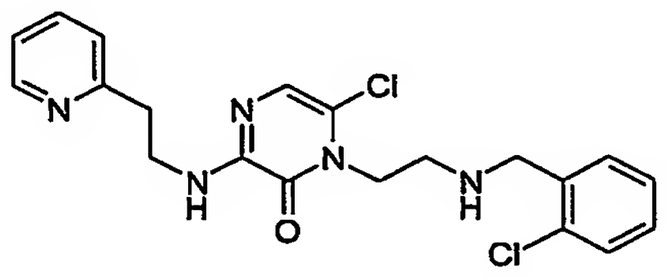
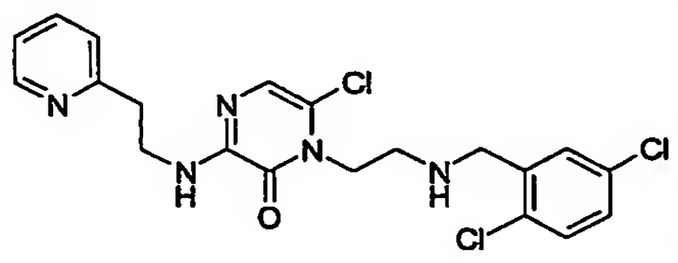
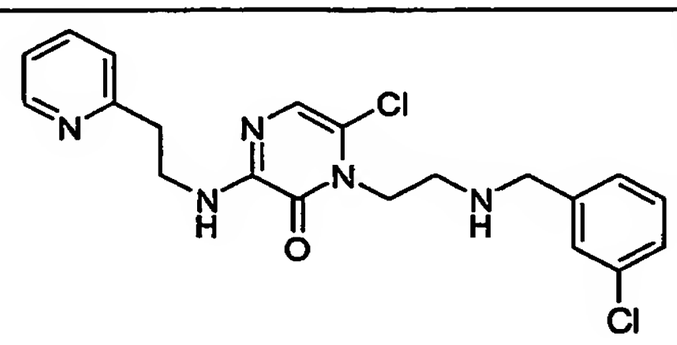
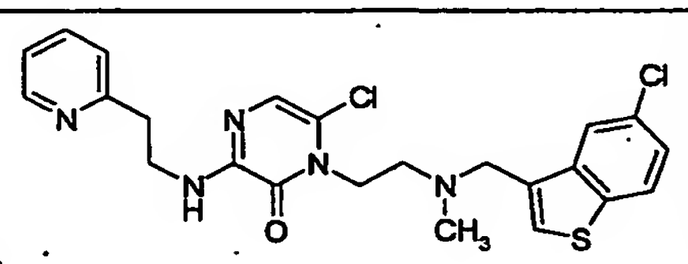
^{1}H-NMR (300 MHz) δ = 2.73-2.78 (m, 2H), 2.98-3.02 (m, 2H), 3.58-3.65 (m, 2H), 3.72 (s, 2H), 4.10-4.15 (m, 2H), 6.68 (s, 1H), 6.69-7.03 (m, 1H), 7.03-7.12 (m, 2H), 7.13-7.35 (m, 4H), 7.63-7.68 (m, 1H), 8.44 (d, 1H).

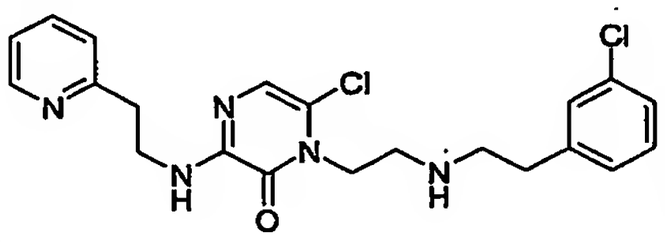
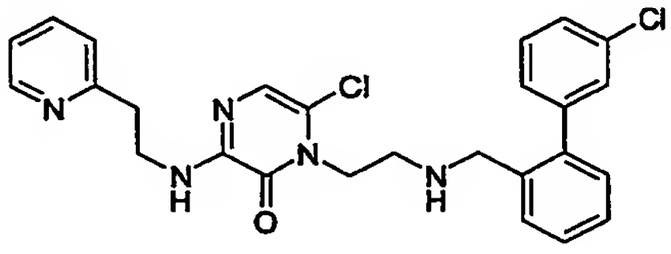
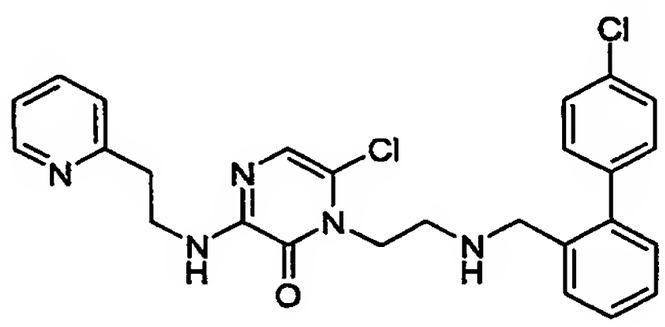
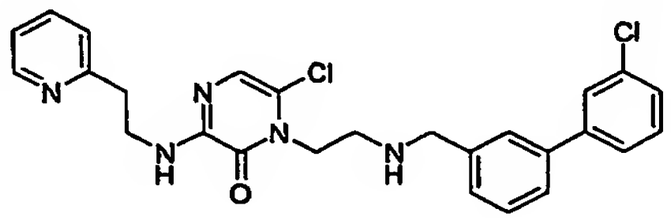
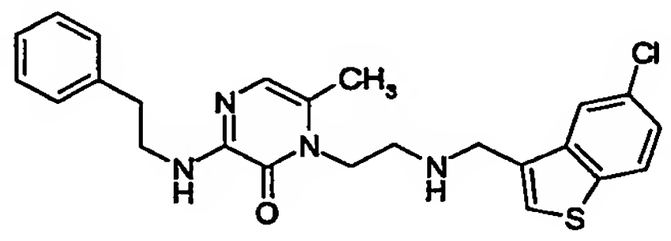
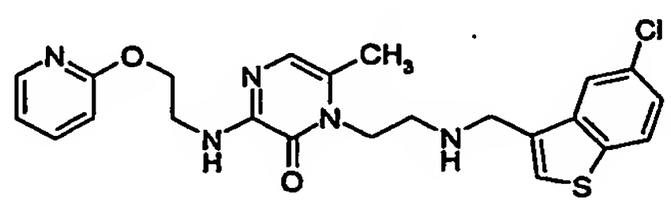
LC/MS (II) (5-95%, 10 min): 2.86, 402 (M+H).

Following the procedure outlined for Example 34, the compounds listed in the Table 1 were prepared.

TABLE 1

Ex.	Structure	Selected ^{1}H-NMR data, (300 MHz) δ	LC/MS data (rt, m/z)

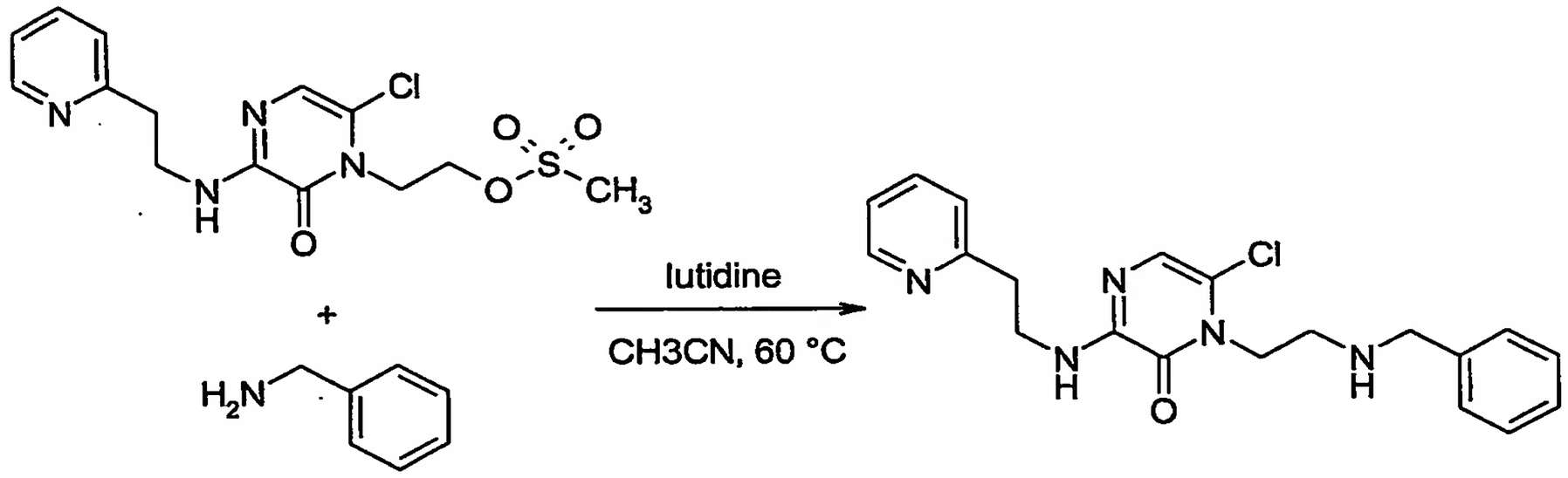
35		2.74-2.79 (m, 2H), 2.97-3.01 (m, 2H), 3.57-3.64 (m, 2H), 3.78 (s, 2H), 4.10-4.14 (m, 2H), 6.68 (s, 1H), 7.02-7.12 (m, 2H), 7.14-7.27 (m, 4H), 7.30-7.39 (m, 1H), 7.61-7.67 (m, 1H), 8.43 (m, 1H)	(I) (5-95%, 10 min) 2.88, 402 (M+H)
36		2.80-2.84 (m, 2H), 2.98-3.03 (m, 2H), 3.58-3.65 (m, 2H), 3.80 (s, 2H), 4.13-4.17 (m, 2H), 6.88 (s, 1H), 7.15-7.43 (m, 7H), 7.65-7.68 (m, 1H), 8.44-8.45 (m, 1H)	(I) (5-95%, 10 min) 2.62, 418 (M+H)
37		2.79-2.83 (m, 2H), 2.98-3.03 (m, 2H), 3.58-3.65 (m, 2H), 3.77 (s, 2H), 4.13-4.17 (m, 2H), 6.88 (s, 1H), 7.21-7.28 (m, 4H), 7.34-7.40 (d, 1H), 7.46-7.47 (d, 1H), 7.62-7.67 (m, 1H), 8.43-8.45 (m, 1H)	(I) (5-95%, 10 min) 2.79, 452 (M+H)
38		2.73-2.78 (m, 2H), 2.98-3.03 (m, 2H), 3.59-3.65 (m, 2H), 3.71 (s, 2H), 4.10-4.14 (m, 2H), 6.88 (s, 1H), 7.16-7.31 (m, 7H), 7.62-7.68 (m, 1H), 8.43-8.45 (m, 1H)	(I) (5-95%, 10 min) 2.74, 418 (M+H)
39		2.33 (s, 3H), 2.61-2.63 (m, 2H), 2.95-2.97 (m, 2H), 3.52-3.59 (m, 2H), 4.07-4.11 (m, 2H), 6.69 (s, 1H), 7.04-7.08 (m, 1H), 7.15-7.30 (m, 2H), 7.51 (s, 1H), 7.62-7.67 (m, 1H), 7.75 (m, 1H), 7.84-7.87 (m, 1H), 8.34-8.45 (m, 1H)	(I) (5-95%, 10 min) 2.92, 488 (M+H)

40			(I) (5-95%, 10 min) 2.73, 432 (M+H)
41		2.68-2.73 (m, 2H), 2.97-3.02 (m, 2H), 3.57 (s, 2H), 3.58-3.64 (m, 2H), 4.03-4.08 (m, 2H), 6.86 (s, 1H), 7.12-7.47 (m, 11H), 7.61-7.67 (m, 1H), 8.44 (d, 1H)	(I) (5-95%, 10 min) 3.14, 494 (M+H)
42		2.68-2.73 (m, 2H), 2.98-3.02 (m, 2H), 3.56 (s, 2H), 3.58-3.65 (m, 2H), 4.03-4.08 (m, 2H), 6.87 (s, 1H), 7.10-7.47 (m, 11H), 7.61-7.66 (m, 1H), 8.43 (d, 1H)	(I) (5-95%, 10 min) 3.12, 494 (M+H)
43		2.77-2.81 (m, 2H), 2.96-3.01 (m, 2H), 3.57-3.64 (m, 2H), 3.78 (s, 2H), 4.12-4.17 (m, 2H), 6.86 (s, 1H), 7.12-7.65 (m, 12H), 8.42-8.44 (m, 1H)	(I) (5-95%, 10 min) 3.83, 494 (M+H)
44		2.17 (s, 3H), 2.78-2.85 (m, 4H), 3.43-3.49 (m, 2H), 3.93-3.99 (m, 4H), 6.58 (s, 1H), 6.62-6.65 (m, 1H), 7.14-7.27 (m, 5H), 7.32-7.35 (dd, 1H), 7.54 (s, 1H), 7.89-7.90 (d, 1H), 7.92-7.95 (d, 1H)	(I) (5-95%, 10 min) 3.36, 453 (M+H)
45		2.17 (s, 3H), 2.78-2.82 (s, 2H), 3.57-3.63 (m, 2H), 3.92-3.99 (m, 4H), 4.35-4.39 (m, 2H), 6.56 (s, 1H), 6.75-6.81 (m, 2H), 6.90-6.94 (m, 1H), 7.32-7.35 (m, 1H), 7.54 (s, 1H), 7.62-7.67 (m, 1H), 7.89-	(I) (5-95%, 10 min) 3.02, 470 (M+H)

		7.94 (m, 2H), 8.09-8.10 (m, 1H)	

Example 46

Step 2 : Method C



1-(2-Benzylamino-ethyl)-6-chloro-3-(2-pyridin-2-yl-ethylamino)-1*H*-pyrazin-2-one.

To a solution of 25.0 mg (0.068 mmol) of crude methanesulfonic acid 2-[6-chloro-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2*H*-pyrazin-1yl]-ethyl ester in 2 mL of acetonitrile is added 11.0 µL (0.100 mmol) of benzylamine, followed by 24.0 µL (0.200 mmol) of 2,6-lutidine are added. The resulting mixture is heated to 60 °C and stirred over night. The reaction mixture is cooled down to room temperature and diluted with 5 mL of dichloromethane, washed with a saturated solution of sodium hydrogencarbonate and brine, dried with sodium sulfate and evaporated under reduced pressure. The crude product is purified by flash chromatography (silica gel, eluent: 5% to 10% methanol in dichloromethane) to yield 13.1 mg (50%) of the title compound.

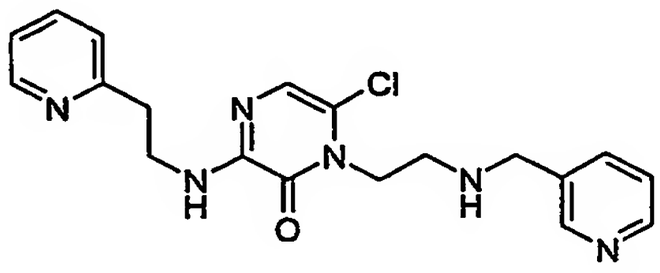
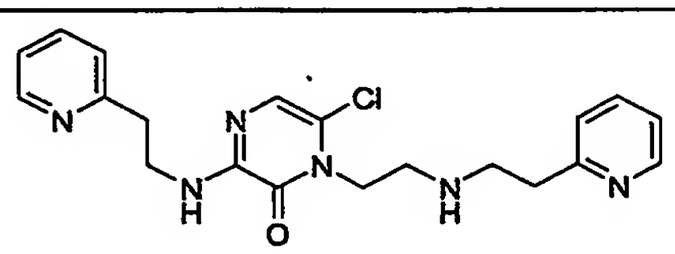
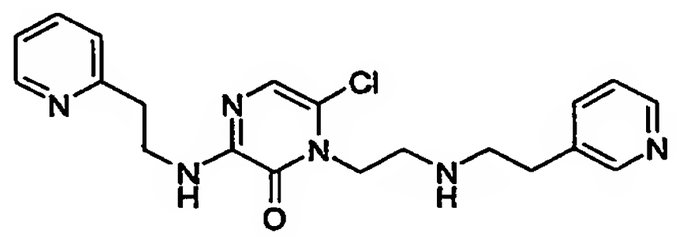
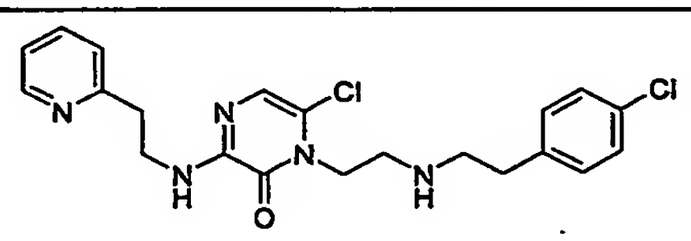
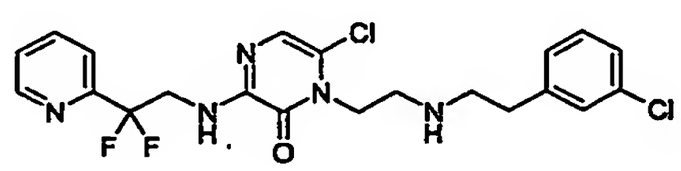
^{1}H-NMR (300 MHz) δ = 2.92-3.02 (m, 4H), 3.59-3.65 (m, 2H), 3.86 (s, 2H), 4.20-4.24 (m, 2H), 6.89 (s, 1H), 7.12-7.41 (m, 8H), 7.62-7.68 (m, 1H), 8.44 (d, 1H).

LC/MS (I) (5-95%, 10 min): 2.41, 384 (M+H).

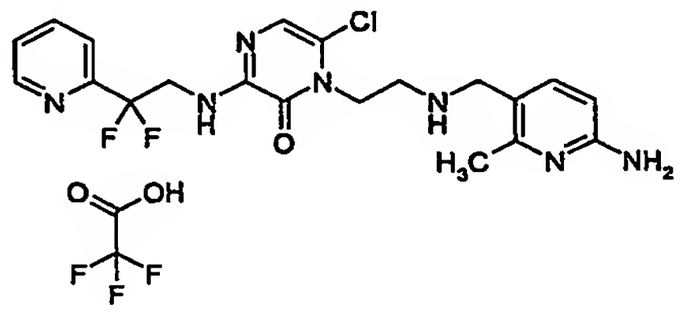
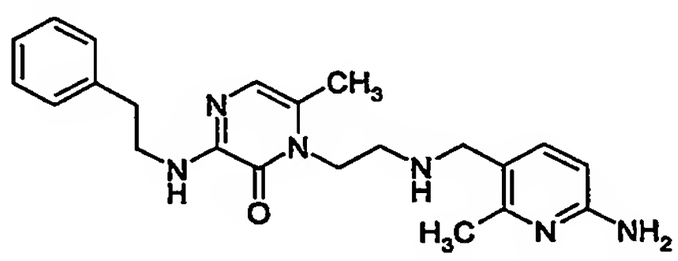
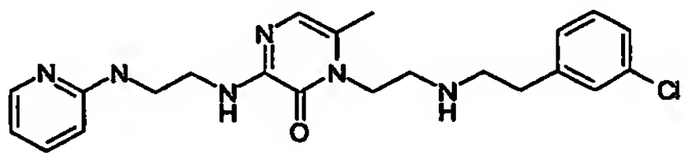
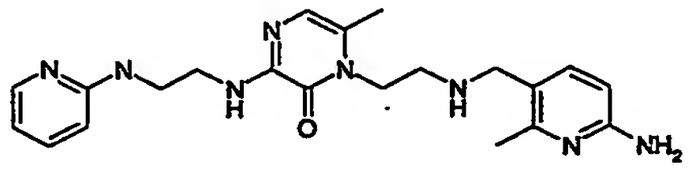
Following the procedure outlined for Example 46, the compounds listed in the Table 2 were prepared.

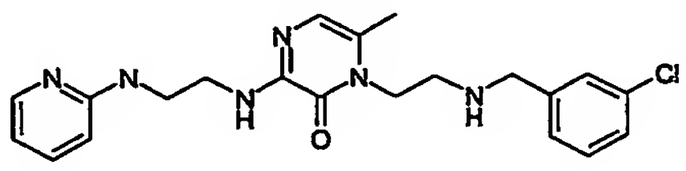
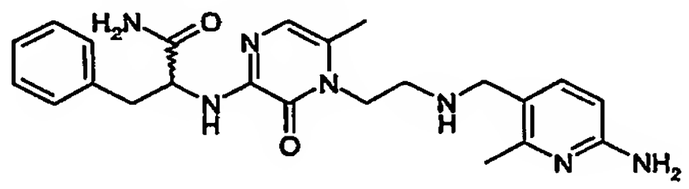
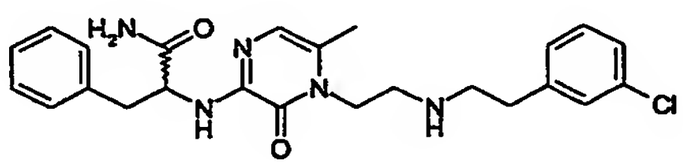
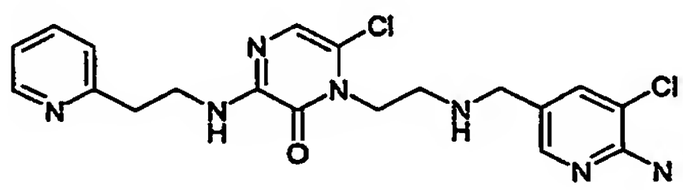
TABLE 2

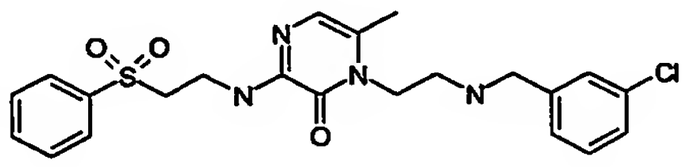
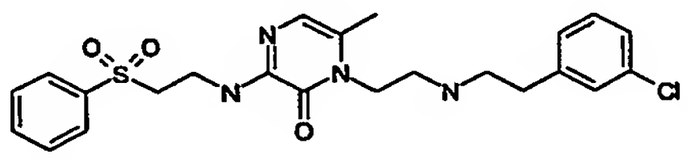
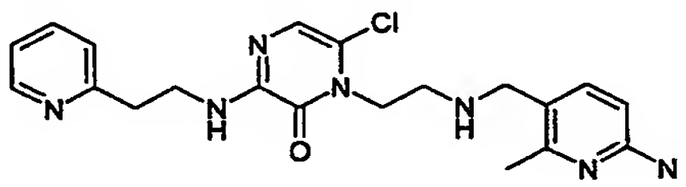
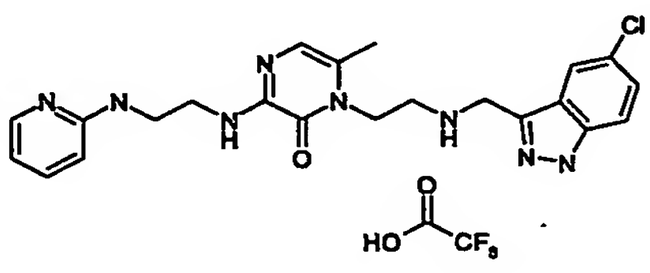
Ex.	Structure	Selected ^{1}H-NMR data, (300 MHz) δ	LC/MS data (rt, m/z)

47		2.77-2.82 (m, 2H), 2.98-3.02 (m, 2H), 3.58-3.64 (m, 2H), 3.75 (s, 2H), 4.12-4.16 (m, 2H), 6.87 (s, 1H), 7.15-7.30 (m, 4H), 7.52-7.69 (m, 2H), 8.33-8.37 (m, 1H), 8.43-8.45 (m, 2H)	(I) (5-95%, 10 min) 1.29, 399 (M+H)
48			(I) (5-95%, 10 min) 1.51, 399 (M+H)
49		2.64-2.69 (m, 2H), 2.76-2.83 (m, 2H), 2.98-3.03 (m, 2H), 3.58-3.65 (m, 2H), 4.07-4.11 (m, 2H), 6.87 (s, 1H), 7.15-7.29 (m, 4H), 7.55-7.57 (m, 1H), 7.63-7.67 (m, 1H), 8.33-8.37 (m, 2H), 8.43-8.45 (m, 1H)	(I) (5-95%, 10 min) 2.11, 399 (M+H)
50		2.62-2.66 (m, 2H), 2.72-2.81 (m, 2H), 2.98-3.03 (m, 2H), 3.59-3.65 (m, 2H), 4.06-4.11 (m, 2H), 6.87 (s, 1H), 7.15-7.30 (m, 7H), 7.63-7.67 (m, 1H), 8.44-8.45 (m, 1H)	(I) (5-95%, 10 min) 2.66, 432 (M+H)
51		2.64-2.69 (m, 2H), 2.77-2.83 (m, 4H), 4.10-4.27 (m, 4H), 4.09-4.28 (m, 4H), 6.87 (s, 1H), 7.11-7.27 (m, 5H), 7.50-7.54 (m, 1H), 7.64-7.67 (m, 1H), 7.92-7.97 (m, 1H),	(I) (5-95%, 10 min) 3.53, 468 (M+H)

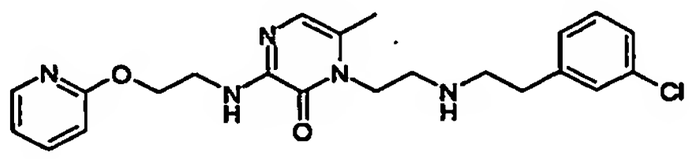
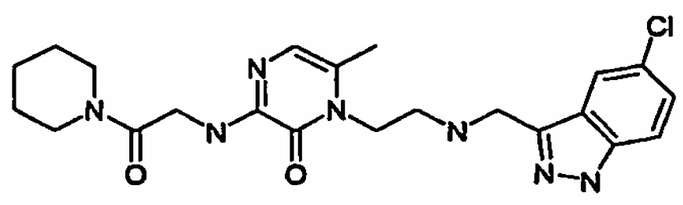
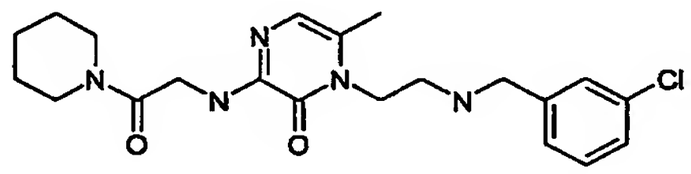
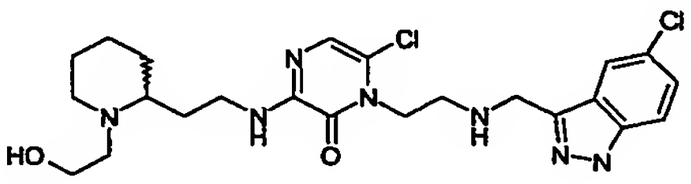
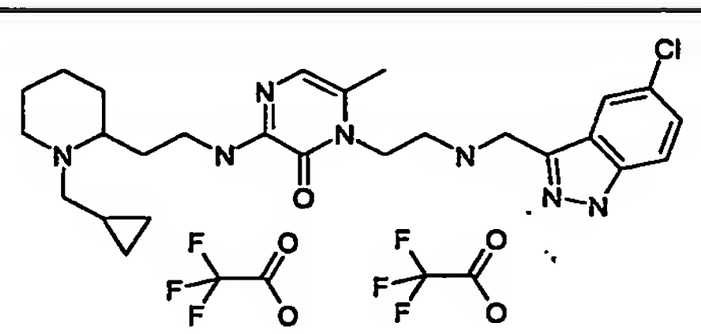
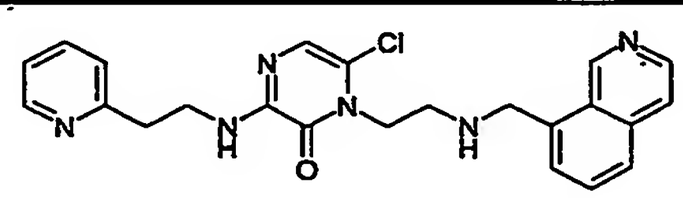
		8.65 (d, 1H)	

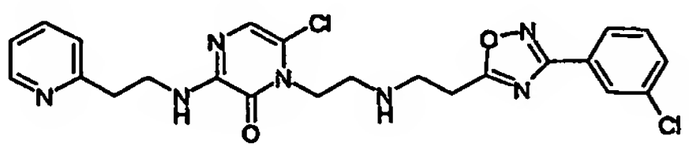
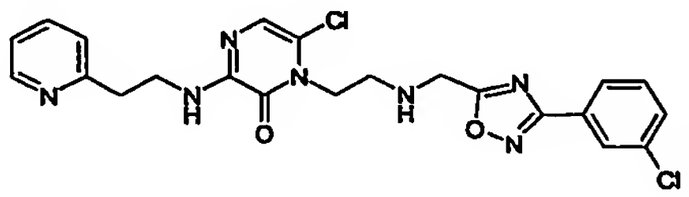
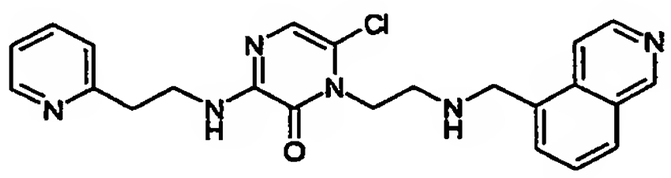
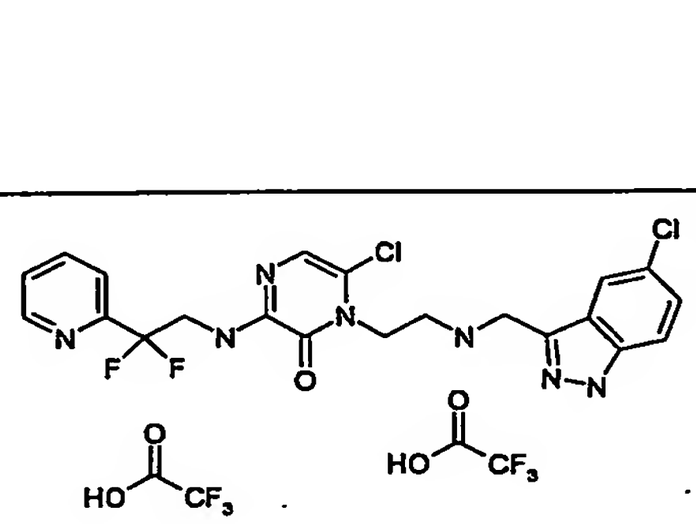
52		2.46-2.54 (s, 3H, under DMSO peak)), 3.26-3.39 (m, 2H), 4.10-4.33 (m, 4H), 4.36-4.40 (m, 2H), 6.80 (d, 1H), 6.96 (s, 1H), 7.28-7.34 (m, 1H), 7.52-7.56 (m, 1H), 7.67 (d, 1H), 7.85 (d, 1H), 7.94-7.99 (m,1H), 8.65 (d, 1H)	(I) (5-95%, 10 min) 2.49, 450 (M+H)
53		2.16 (s, 3H), 2.22 (s, 3H), 2.71-2.73 (m, 2H), 2.75-2.85 (m, 2H), 3.43-3.50 (m, 4 H), 3.92-3.97 (m, 2H), 5.51 (bs, 2H), 6.16 (d, 1H), 6.59 (s, 1H), 6.65-6.69 (m, 1H), 7.12-7.27 (m, 7H)	(I) (5-95%, 10 min) 2.26, 393 (M+H)
54		2.13 (s, 3H), 2.54-2.83 (m, 5H), 3.30-3.45 (m, 5H), 3.79-3.96 (m, 2H), 6.35-6.47 (m, 2H), 6.48-6.64 (m, 2H), 6.90-7.03 (m, 1H), 7.08-7.40 (m, 5H), 7.87-8.00 (m, 1H)	(I) (5-95%, 10 min) 2.53, 427 (M+H)
55		2.08 (s, 3H), 2.16 (s, 3H), 2.70-2.84 (m, 2H), 3.32-3.44 (m, 4H), 3.56 (s, 2H), 3.90-4.02 (m, 2H), 6.12-6.22 (m, 1H), 6.37-6.47 (m, 2H), 6.47-6.63 (m, 2H), 6.92-7.02 (m, 1H), 7.15-7.22 (m, 1H), 7.27-7.35 (m, 1H), 7.89-7.95 (m, 1H)	(I) (5-95%, 10 min) 1.80 409 (M+H)

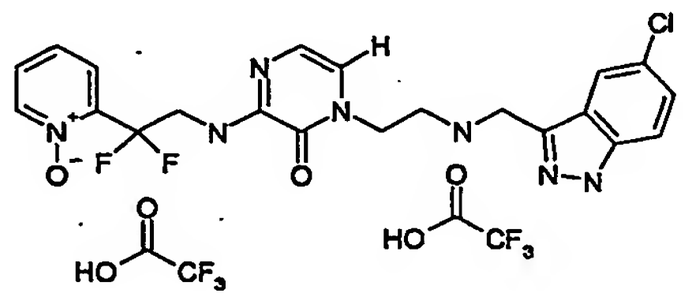
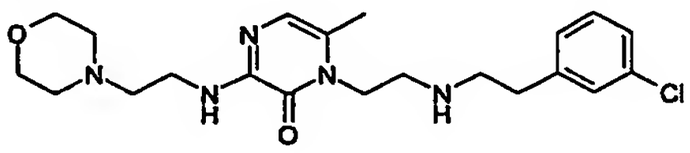
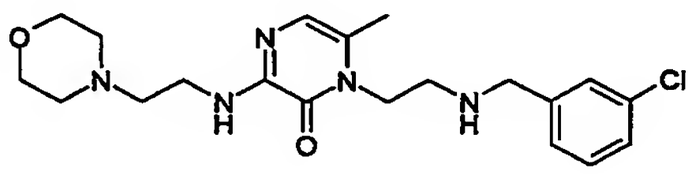
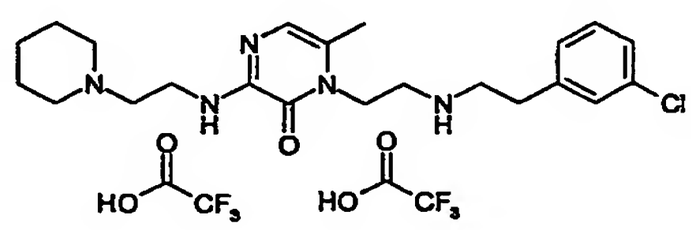
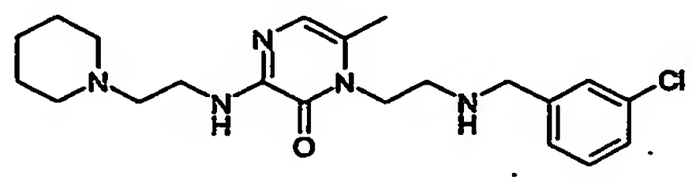
56		2.15 (s, 3H), 2.63-2.77 (m, 2H), 3.31-3.49 (m, 4H), 3.68 (s, 2H), 3.83-4.02 (m, 2H), 6.29-6.66 (m, 4H), 6.66-6.86 (m, 1H), 7.11-7.40 (m, 5H), 7.84-7.99 (m, 1H)	(I) (5-95%, 10 min) 2.18, 413 (M+H)
57			(I) (5-95%, 10 min) 3.15, 440 (M+H)
58		2.15 (s, 3H), 2.21 (s, 3H), 2.53-2.67 (m, 2H), 2.91-3.15 (m, 2H), 3.50 (s, 2H), 3.86-4.01 (m, 2H), 4.44-4.61 (m, 1H), 6.10-6.24 (m, 1H), 6.38-6.52 (m, 1H), 6.58 (s, 1H), 7.00 (bs, 1H), 7.06-7.29 (m, 5H), 7.33-7.44 (bs, 2H)	(I) (5-95%, 10 min) 2.31 436 (M+H)
59			(I) (5-95%, 10 min) 3.23, 454 (M+H)
60		3.06-3.21 (m, 4H), 3.57-3.66 (m, 2H), 4.06 (s, 2H), 4.30-4.35 (m, 2H), 6.85 (s, 1H), 7.44-7.50 (m, 1H), 7.62-7.81 (m, 3H), 7.94-8.02 (m, 1H), 8.15-8.20 (m, 1H), 8.55-8.70 (m, 1H)	(I) (5-95%, 5 min) 1.07, 434 (M+H)

61		2.15 (s, 3H), 2.65-2.70 (m, 2H), 3.46-3.60 (m, 4H), 3.68 (s, 2H), 3.84-3.96 (m, 2H), 6.53 (s, 1H), 6.76-6.82 (m, 1H), 7.15-7.32 (m, 4H), 7.52-7.62 (m, 2H), 7.62-7.71 (m, 1H), 7.79-7.87 (m, 2H)	(I) (5-95%, 5 min) 1.93, 461 (M+H)
62		2.14 (s, 3H), 2.61-2.78 (m, 6H), 3.46-3.60 (m, 4H), 3.81-3.92 (m, 2H), 6.52 (s, 1H), 6.75-6.84 (m, 1H), 7.07-7.14 (m, 1H), 7.15-7.27 (m, 3H), 7.53-7.62 (m, 2H), 7.64-7.72 (m, 1H), 7.80-7.87 (m, 2H)	(I) (5-95%, 5 min) 2.13, 475 (M+H)
63		2.54 (s, 3H), 3.03-3.19 (m, 2H), 3.26-3.38 (m, 2H), 3.59-3.78 (m, 2H), 4.15 (s, 2H), 4.29-4.46 (m, 2H), 6.81 (d, 1H), 6.91 (s, 1H), 7.39-7.60 (m, 3H), 7.83-7.92 (m, 1H) 7.94-8.06 (m, 1H), 8.53-8.66 (m, 1H)	(I) (5-90%, 5 min) 1.60 min 414 (M+H)
64		2.19 (s, 3H), 3.30-3.40 (m, 2H), 3.79-3.96 (m, 2H), 4.22-4.26 (m, 2H), 4.38-4.40 (m, 2H), 4.58 (s, 2H), 6.67 (s, 1H), 6.77-6.79 (m, 1H), 7.35-7.40 (m, 2H), 7.55-7.61 (m, 3H), 7.93-8.03 (m,	(I) (5-90%, 5 min) 1.74 453 (M+H)

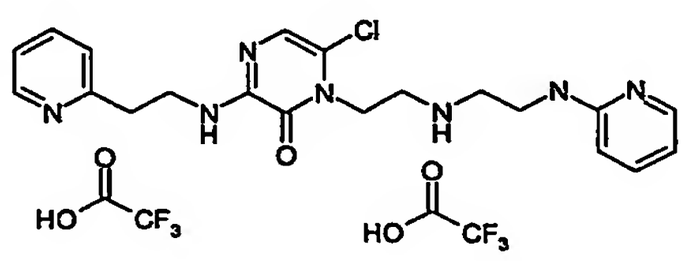
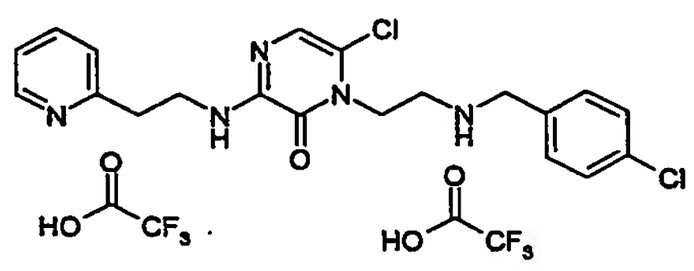
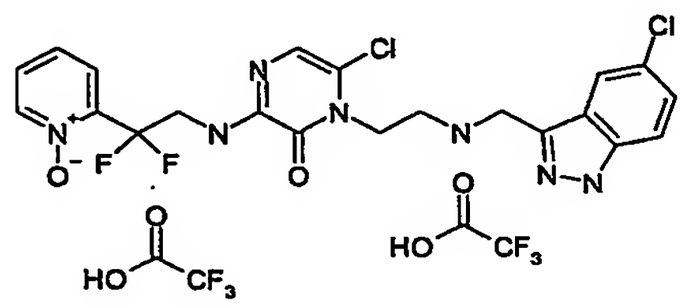
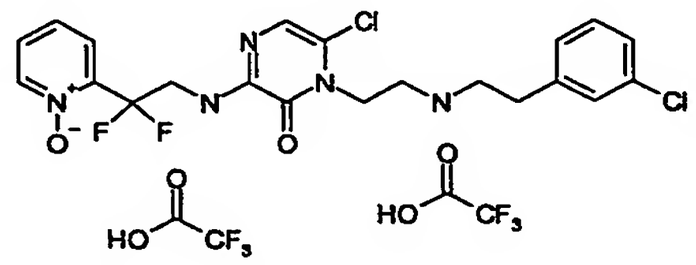
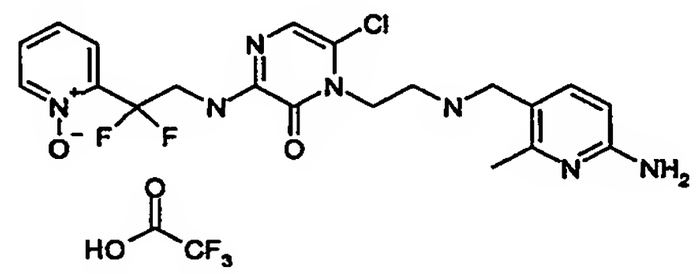
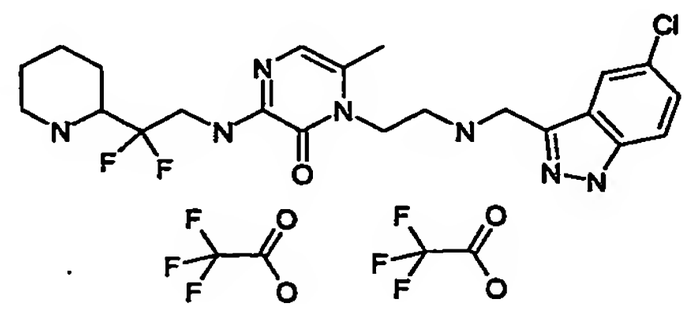
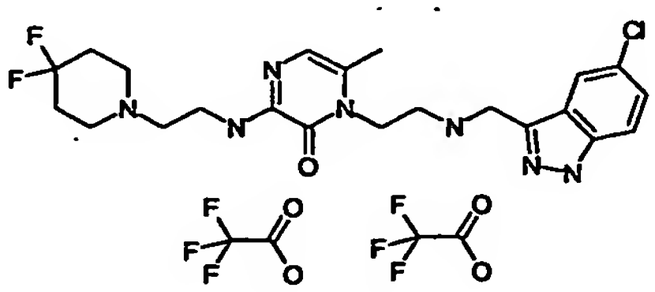
		2H)	

65			(I) (5-95%, 5 min) 2.03 428 (M+H)
66			(I) (5-95%, 5 min) 1.85 458 (M+H)
67			(I) (5-95%, 5 min) 1.85 418 (M+H)
68			(I) (5-60%, 5 min) 3.35 508 (M+H) chiral separation (15:85:0, 0.7mL/min): 23.45 (E1) 28.48 (E2)
69			(I) (5-60%, 5 min) 2.57 498 (M+1)
70		3.05-3.15 (m, 4H), 3.75-3.86 (m, 2H), 4.25-4.35 (m, 2H), 4.38 (s, 2H), 6.50-6.60 (m, 1H), 6.89 (s, 1H), 7.10-7.20 (m, 2H), 7.50-7.76 (m, 5H) 8.50-8.62 (m, 2H), 9.60 (s, 1H)	

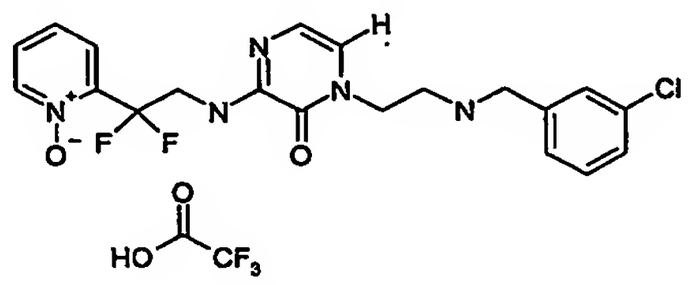
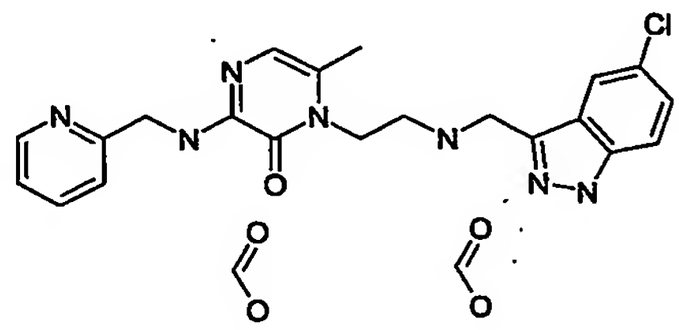
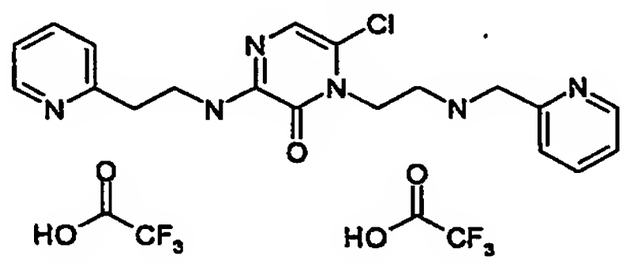
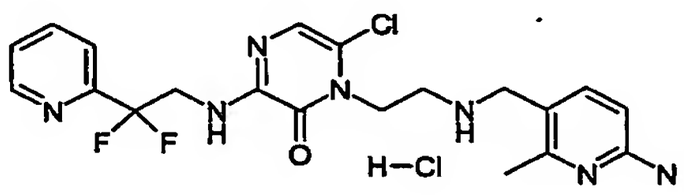
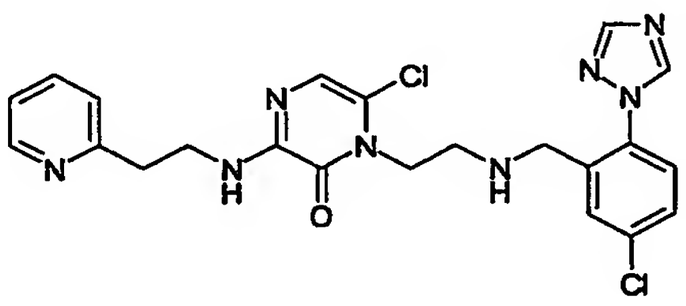
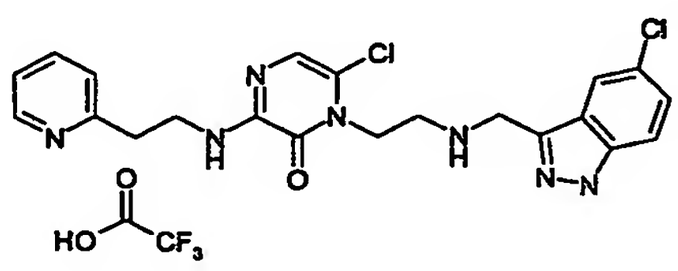
71		2.95-3.05 (m, 2H), 3.05-3.15 (m, 4H), 3.15-3.22 (m, 2H), 3.70-3.75 (m, 2H), 4.20-4.30 (m, 2H), 6.50-6.60 (m, 1H), 6.90 (s, 1H), 7.10-7.20 (m, 2H), 7.37-7.55 (m, 2H) 7.58-7.65 (m, 1H), 7.92-7.80 (m, 1H), 8.09 (s, 1H), 8.55-8.60 (m, 1H)	
72		3.05-3.15 (m, 4H), 3.75-3.85 (m, 2H), 4.15 (s, 2H), 4,25-4,34 (m, 2H), 6.50-6.60 (m, 1H), 6.90 (s, 1H), 7.10-7.20 (m, 2H), 7.40-7.55 (m, 2H) 7.58-7.62 (m, 1H), 7.97-8.00 (m, 1H), 8.10 (s, 1H), 8.57-8.60 (m, 1H)	
73		3.04-3.12 (m, 4H), 3.70-3.85 (m, 2H), 4.25 (s, 2H), 4.28-4.32 (m, 2H), 6.50-6.60 (m, 1H), 6.85 (s, 1H), 7.10-7.20 (m, 2H), 7.50-7.60 (m, 3H), 7.86-7.90 (m, 2H), 8.50-8.60 (m, 2H), 9.22 (s, 1H)	
74		3.35-3.50 (bs, 2H), 4.12-4.34 (m, 2H), 4.34-4.42 (m, 2H), 4.59 (bs, 2H), 6.94 (s, 1H), 7.22-7.35 (m, 1H), 7.35-7.46 (m, 1H), 7.47-7.70 (m, 3H), 7.87-7.11 (m, 2H), 8.60-8.754 (m, 1H)	(I) (5-60%, 10 min) 5.63 494 (M+H)

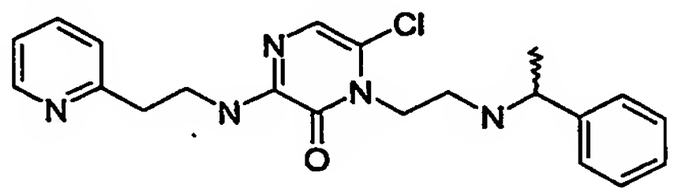
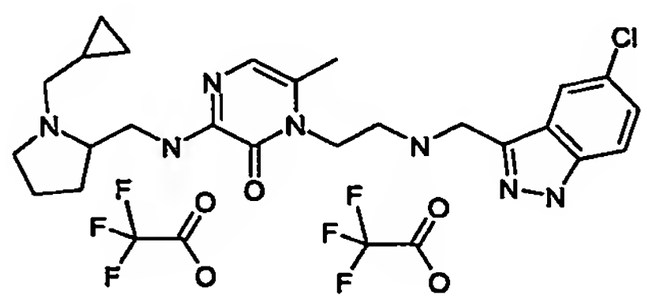
75		3.30-3.45 (m, 2H), 4.10-4.20 (m, 2H), 4.32-4.66 (m, 4H), 6.63-6.64 (m, 1H), 6.73-6.74 (m, 1H), 7.17-7.25 (m, 1H), 7.30-7.44 (m, 2H), 7.44-7.62 (m, 4H), 7.99-8.06 (m, 1H), 8.27-8.34 (m, 1H)	(I) (10-60%, 10 min) 2.84 476 (M+H)
76		2.15 (s, 3H), 2.33- 2.41 (m, 4H), 2.61-2.71 (m, 2H), 2.71-2.82 (m,4H), 3.25 (bs, 2H), 3.25-3.30 (m, 2H), 3.49-3.61 (m, 4H), 3.85-3.97 (m, 2H), 6.55 (s, 1H), 7.10-7.36 (m, 4H)	(I) (5-90%, 5 min) 1.81 420 (M+H)
77		2.16 (s, 3H), 2.35- 2.43 (m, 2H), 2.65-2.82 (m, 2H), 3.14-3.36 (m, 6H), 3.50-3.60 (m, 4H), 3.73 (s,2H), 3.89-4.02 (m, 2H), 6.57 (s, 1H), 7.16-7.41 (m, 4H)	(I) (5-90%, 5 min) 1.74 406 (M+H)
78		1.40-1.80 (m, 6H), 2.20 (s, 3H), 2.86- 2.97 (m, 3H), 3.02-3.09 (m, 2H), 3.15-3.32 (m, 7H), 3.55-3.67 (m, 2H), 4.15-4.27 (m, 2H), 6.66 (s, 1H), 7.18-7.42 (m, 5H)	(I) (5-90%, 5 min) 2.06 418 (M+H)
79		1.31-1.44 (m, 2H), 01.44-1.53 (m, 4H), 2.16 (s, 3H), 2.29- 2.37,0 (m, 4H), 2.39-2.47 (m, 2H), 2.63-2.73 (m, 2H), 3.20-3.39	(I) (5-90%, 5 min) 1.93 404 (M+H)

		(m, 2H), 3.69 (s, 2H), 3.89-4.02 (m, 2H), 6.46-6.55 (m,1H), 6.56 (s, 1H), 7.13-7.36 (m, 4H)	

80			(I) (5-90%, 5 min) 1.93 414 (M+H)
81			(I) (5-90%, 5 min) 1.84 418 (M+H)
82			(I) (5-95%, 10 min) 2.95 510 (M+H)
83			(I) (5-95%, 10 min) 3.19 484 (M+H)
84			(I) (5-95%, 5 min) 1.66 466 (M+H)
85			(I) (10-60%, 8 min) 2.43 480 (M+H) chiral separation (15:85:0, 0.7mL/min):20 .16 (E1) 23.85 (E2)
86		2.20 (s, 3H), 2.22-2.40 (m, 4H), 3.28-3.35 (m, 4H), 3.35-3.40 (m, 4H), 3.56-3.67 (m, 2H), 4.19-	(I) (10-60%, 8 min) 2.57 480 (M+H)

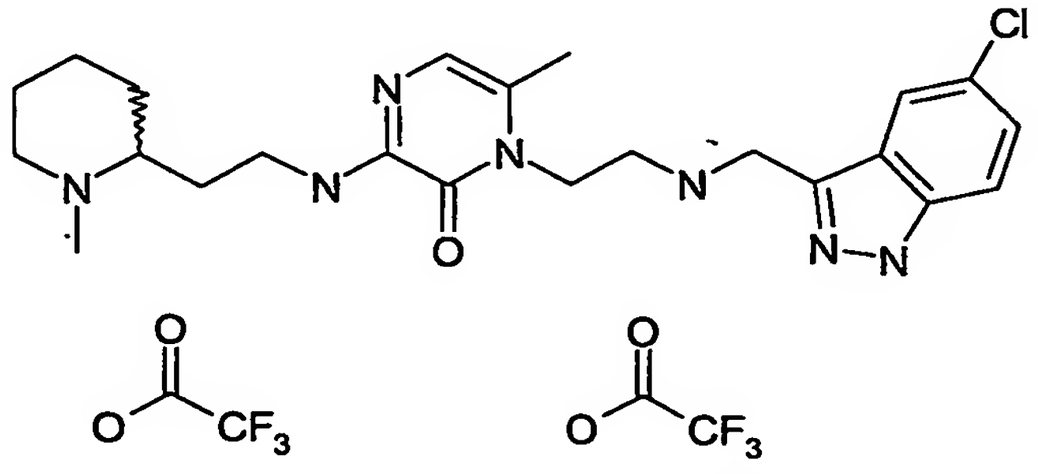
		4.31 (m, 2H), 4.58 (s, 2H), 6.65 (s, 1H), 7.21-7.31 (m, 1H), 7.33-7.42 (m, 1H), 7.56-7.64 (m, 1H), 8.01-8.06 (m, 1H)	

87			(I) (1-30%, 8 min) 6.10 436 (M+H)
88			(I) (1-30%, 8 min) 6.23 424 (M+H)
89		3.08-3.17 (m, 2H), 3.32-3.40 (m, 2H), 3.60-3.71 (m, 2H), 4.37 (s, 2H), 4.39-4.47 (m, 2H), 6.90 (s, 1H), 7.36-7.58 (m, 5H), 7.80-7.89 (m, 1H), 7.97-8.07 (m, 1H), 8.55-8.62 (m, 1H)	(I) (5-90%, 5 min) 1.59 385 (M+H)
90			(I) (5-95%, 10 min) 2.49 450 (M+H)
91		3.21-3.26 (m, 2H), 3.30-3.34 (m, 2H), 3.60-3.70 (m, 2H), 4.25 (s, 2H), 4.34-4.38 (m, 2H), 6.89 (s, 1H), 7.55-7.59 (m, 1H), 7.70-7.82 (m, 5H), 8.24 (s, 1H), 8.27-8.33 (m, 1H), 8.70-8.72 (m, 1H), 9.01 (s, 1H)	(I) (5-70%, 10 min) 2.72 485 (M+H)
92		3.11-3.16 (m, 3H), 3.35-3.45 (m, 2H), 3.60-3.70 (m, 2H), 4.36-4.43 (m, 2H), 4.59 (s, 1H), 6.90 (s, 1H), 7.36-7.39 (m, 1H),	(I) (5-90%, 5 min) 1.94 458 (M+H)

		7.43-7.62 (m, 4H), 7.97-8.03 (m, 2H), 8.56-8.58 (m, 1H)	
93		1.54-1.56 (d, 3H), 2.90-3.05 (m, 1H), 3.17-3.22 (m, 3H), 3.60-3.72 (m, 2H), 4.25-4.40 (m, 2H), 4.40-4.50 (m, 1H), 6.83 (s, 1H), 7.39-7.60 (m, 5H), 7.69-7.75 (m, 3H), 8.20-8.30 (m, 1H), 8.65-8.70 (m, 1H)	(I) (5-95%, 3 min) 1.52 398 (M+H)
94			(I) (10-60%, 8 min) 2.74 470 (M+H) chiral separation (85:15:0, 0.7mL/min): 38.92 (E1) 40.96 (E2)

Example 95

5



1-{2-[(5-Chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-6-methyl-3-[2-(1-methyl-piperidin-2-yl)-ethylamino]-1H-pyrazin-2-one

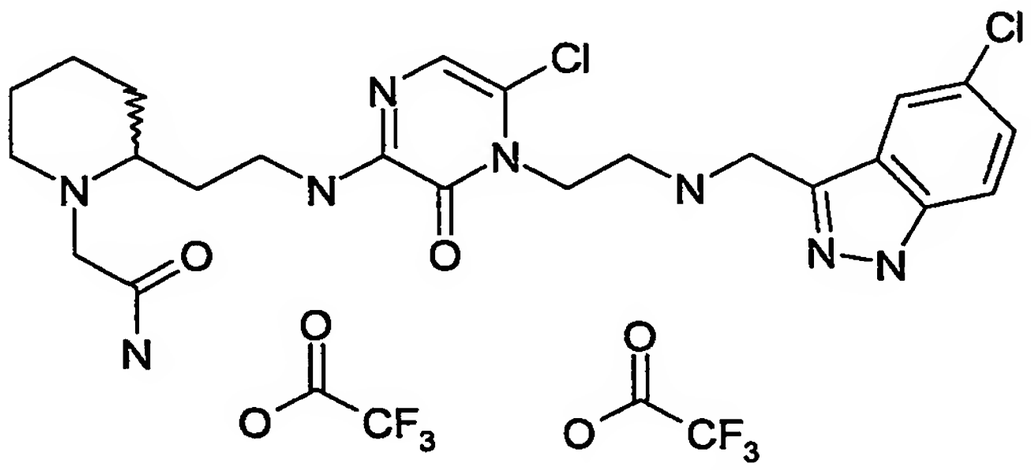
Obtained according to method C, using MeOH as co-solvent in the reaction.

^{1}H-NMR (200 MHz) δ = 1.35-1.53 (m, 2H), 1.54-1.83 (m, 5H), 2.19 (s, 3H) 2.65-2.83 (m, 3H), 3.16 (s, 3H), 3.27-3.42 (m, 4H), 4.18-4.27 (m, 2H), 4.34-4.45 (m, 1H), 4.59 (s,2H), 6.64 (s, 1H), 7.25-7.33 (m, 1H), 7.33-7.43 (m, 1H), 7.51-7.66 (m, 1H), 7.98-8.08 (m, 1H).

LC/MS (I) (5-90%, 5 min): 2.02, 458 (M+H).

Chiral separation (15:85:0, 0.7mL/min): 18.7 (E1); 21.8 (E2).

Example 96

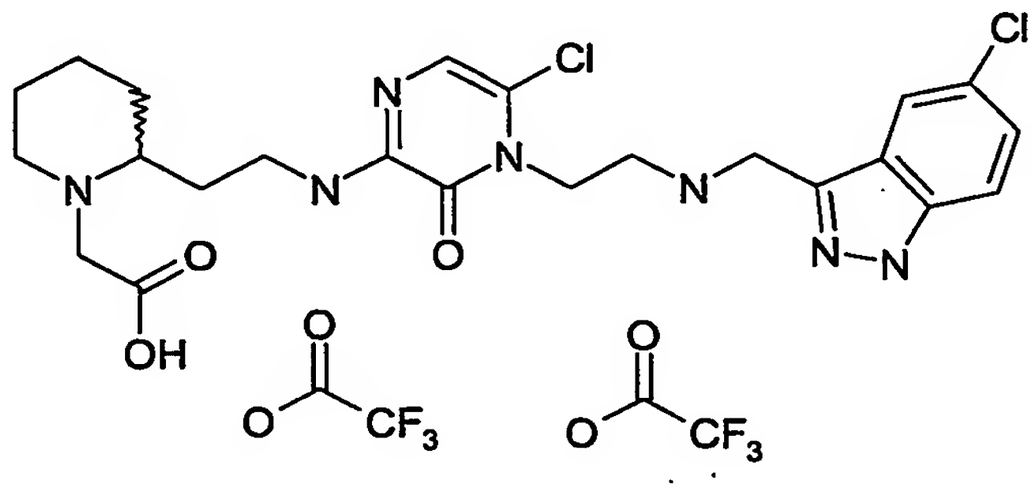


2-{2-[2-(5-Chloro-4-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidin-1-yl}-acetamide

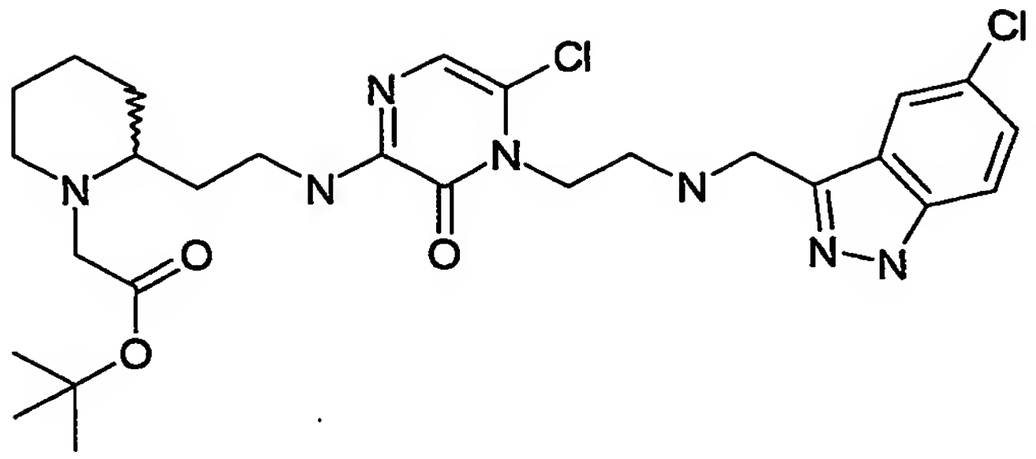
Obtained according to method C, using MeOH as co-solvent in the reaction.

LC/MS (I) (5-95%, 10 min): 2.68, 521 (M+H).

Example 97



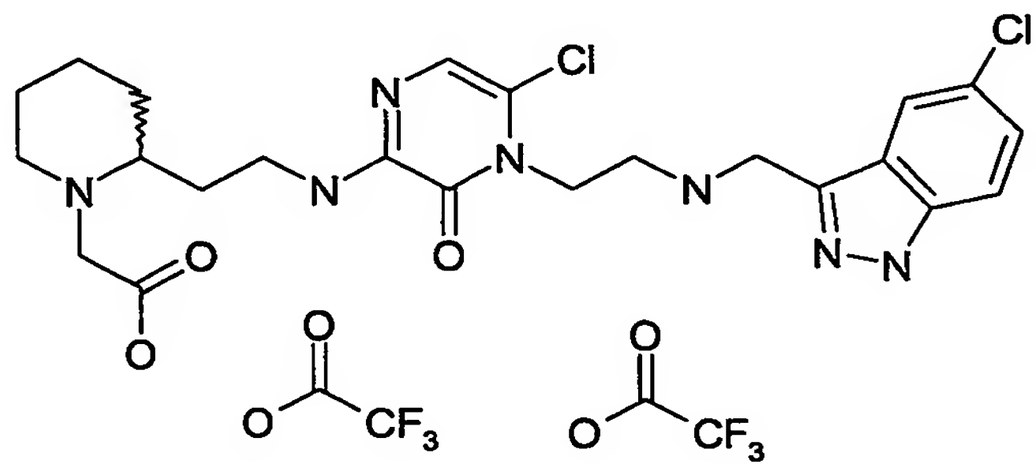
Step 2



{2-[2-(5-Chloro-4-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidin-1-yl}-acetic acid tert-butyl ester

Obtained according to method C, using MeOH as cosolvent in the reaction.
LC/MS (I) (5-90%, 5 min): 1.93, 578 (M+H).

Step 3

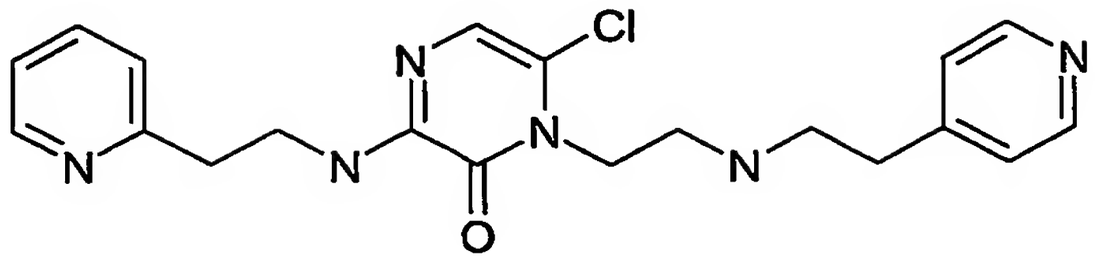


{2-[2-(5-Chloro-4-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidin-1-yl}-acetic acid

{2-[2-(5-Chloro-4-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidin-1-yl}-acetic acid tert-butyl ester (46.0 mg, 0.101 mmol) is dissolved in 2 mL of a 20% solution of TFA in DCM. After 30 min the solvent is evaporated and the crude product is purified by HPLC.

^{1}H-NMR (200 MHz) δ = 1.33-1.51 (m, 1H), 1.55-1.83 (m, 5H), 1.83-2.10 (m, 2H), 3.07-3.18 (m, 1H), 3.24-3.40 (m, 6H), 3.94-4.03 (m, 1H), 4.10-4.20 (m, 1H), 4.40-4.47 (m, 2H), 4.59 (bs, 2H), 6.89 (s, 1H), 7.35-7.42 (m, 1H), 7.47-7.52 (m, 1H), 7.57-7.63 (m, 1H), 8.00-8.05 (m, 1H).
LC/MS (I) (5-5%, 5 min): 2.67, 522 (M+H).

Example 98

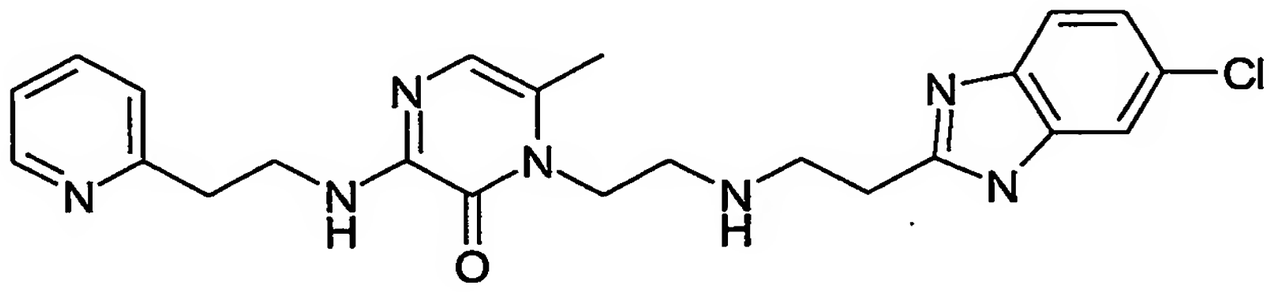


6-Chloro-3-(2-pyridin-2-yl-ethylamino)-1-[2-(2-pyridin-4-yl-ethylamino)-ethyl]-1H-pyrazin-2-one

Obtained according to method C, using polymer-supported collidine in place of lutidine as base.

LC/MS (I) (5-95%, 10 min): 1.90, 399 (M+H).

Example 99



Step 1

Methanesulfonic acid 2-[6-methyl-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2H-pyrazin-1-yl]-ethyl ester is obtained according to example 32.

Step 2

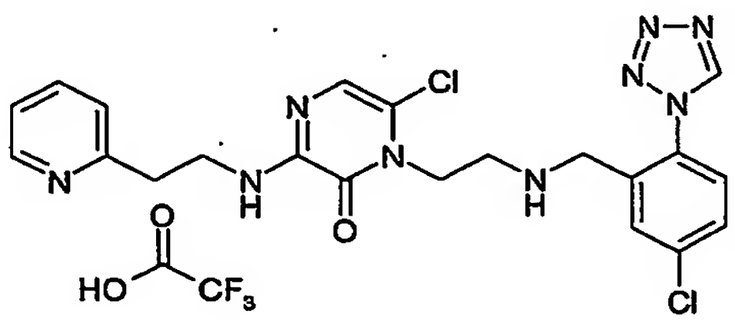
Methanesulfonic acid 2-[6-methyl-2-oxo-3-(2-pyridin-2-yl-ethylamino)-2H-pyrazin-1-yl]-ethyl ester and 2-(6-chloro-1H-benzoimidazol-2-yl)-ethylamine are dissolved in dry methanol and 170 mg of MP-carbonate resin (Separtis GmbH) is added. The mixture is heated at 50 °C overnight and after cooling down to room temperature the resin is filtered off. The organic solvent is evaporated by reduced pressure and the crude product is purified by HPLC-chromatography.

^{1}H-NMR (200 MHz) δ = 2.21 (s, 3H), 3.17-3.21 (m, 2H), 2.26-3.33 (m, 4H), 3.50-3.55 (m, 2H), 3.69-3.73 (m, 2H), 4.20-4.25 (m, 2H) 6.64 (s, 1H), 7.22-7.25 (m, 1H), 7.53-7.67 (m, 4H), 8.12-8.17 (m, 2H), 8.64-8.66 (m, 1H)

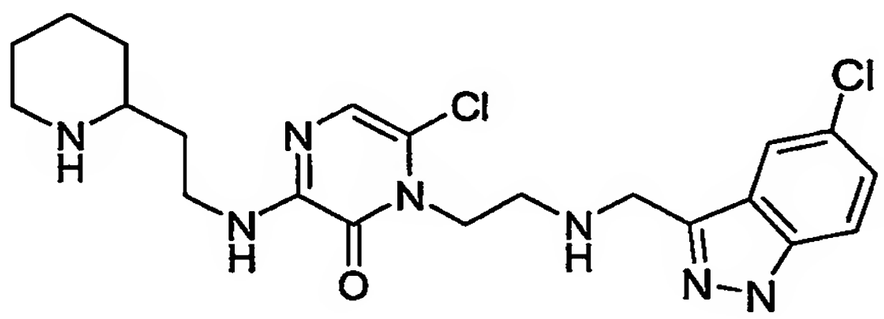
LC/MS (I) (5-70%, 10 min): 3.03, 452 (M+H).

Following the procedure outlined for Example 99 the compounds listed in the Table 3 were prepared.

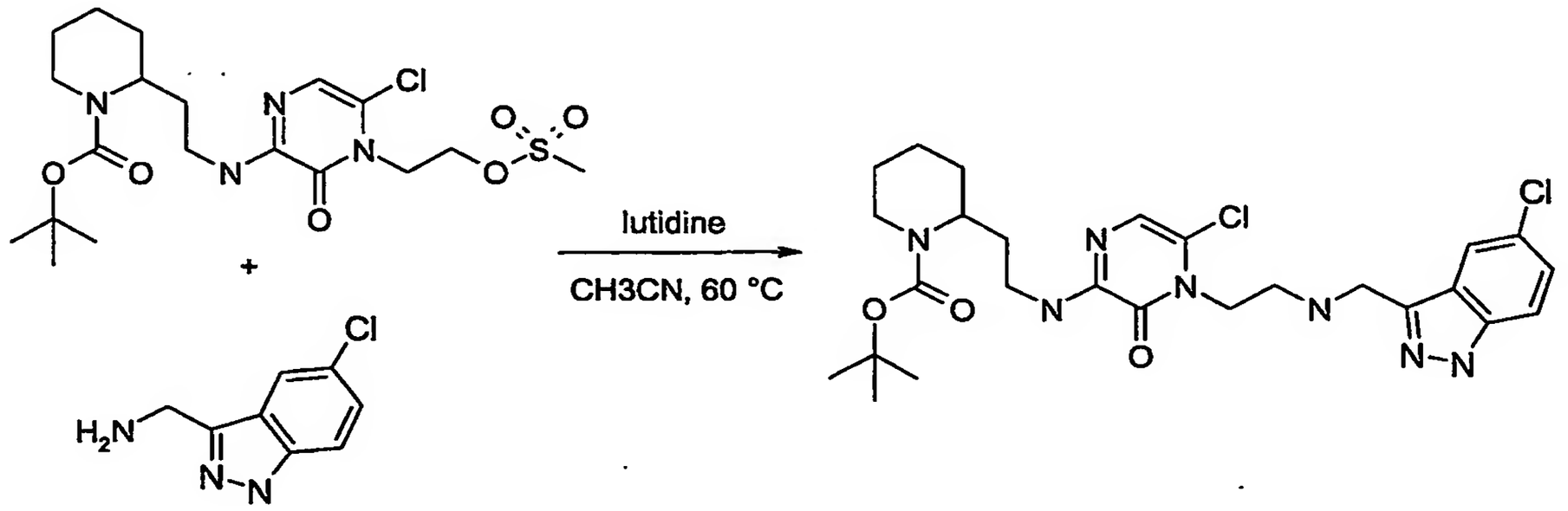
TABLE 3

100		3.18-3.25 (m, 2H), 3.25-3.32 (m, 2H), 3.65-3.75 (m, 2H), 4.21 (s, 2H), 4.31-4.35 (m, 2H), 6.87 (s, 1H), 7.70-7.82 (m, 4H), 7.91-7.93 (m, 1H), 8.25-8.35 (m, 1H), 8.68-8.85 (m, 1H), 9.83 (s, 1H)	(I) (5-90%, 5 min) 1.84 486 (M+H)

Example 101



Step 1

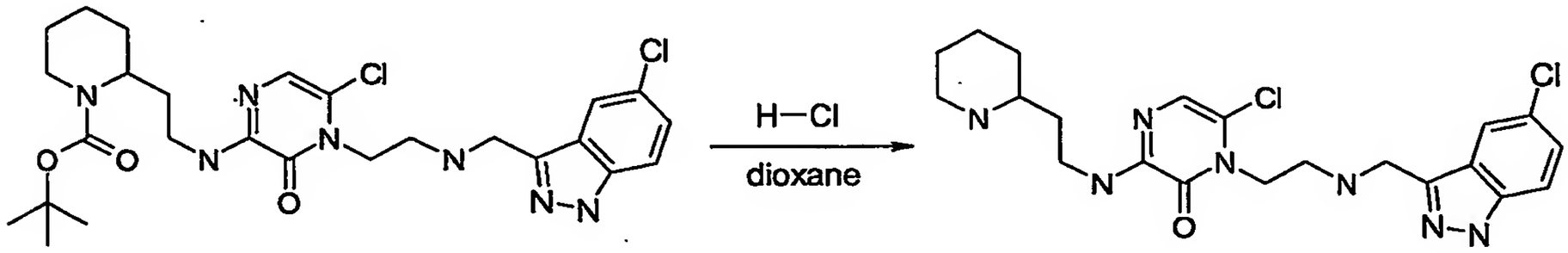


2-[2-(5-Chloro-4-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester

Obtained from 2-{2-[5-chloro-4-(2-methanesulfonyloxy-ethyl)-3-oxo-3,4-dihydro-pyrazin-2-ylamino]-ethyl}-piperidine-1-carboxylic acid tert-butyl ester and C-(5-chloro-1H-indazol-3-yl)-methylamine according to the procedure described for Example 24.

1.20-1.37 (m, 2H), 1.37 (s, 9H),1.41-1.68 (m, 5H), 1.84-1.97 (m, 1H), 2.68-2.86 (m, 3H), 3.11-3.29 (m, 3H), 3.75-3.86 (m, 1H), 4.01-4.04 (s, 2H), 4.11-4.17 (m, 2H), 6.82 (s, 1H), 7.03-7.10 (m, 1H), 7.22-7.28 (m, 1H), 7.40-7.45 (m, 1H), 7.82-7.86 (m, 1H).
LC/MS (I) (5-970%, 5 min): 2.68, 564 (M+H).

Step 2



6-Chloro-1-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-(2-piperidin-2-yl-ethylamino)-1H-pyrazin-2-one

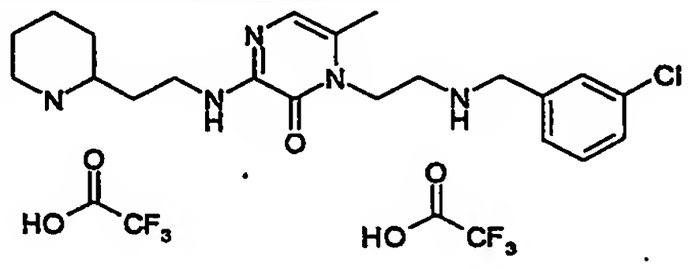
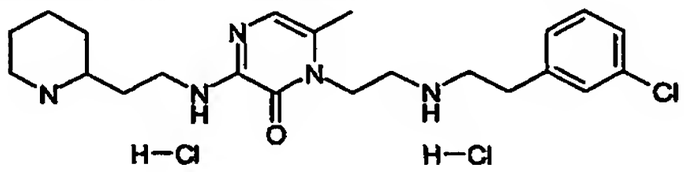
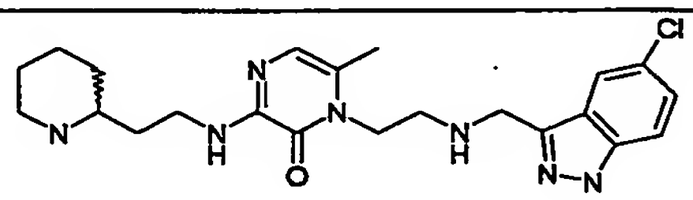
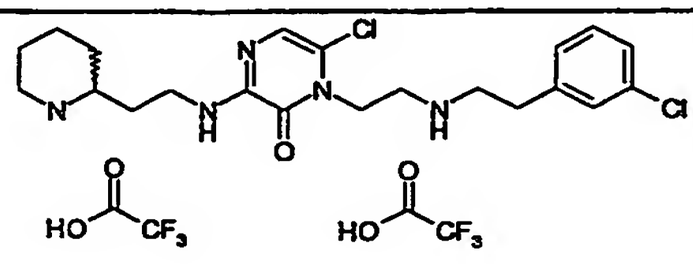
2-[2-(5-Chloro-4-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-oxo-3,4-dihydro-pyrazin-2-ylamino)-ethyl]-piperidine-1-carboxylic acid tert-butyl ester is dissolved in a 4M solution of hydrochloric acid in dioxane and stirred at room temperature. After 2h the solvent is evaporated and the product is purified by HPLC.

1.25-1.65 (m, 3H), 1.67-1.80 (m, 3H), 1.82-1.96 (m, 2H), 2.70-2.90 (m, 1H), 2.92-3.01 (m, 1H), 3.18-3.30 (m, 1H), 3.32-3.46 (m, 4H), 4.35-4.50 (m, 2H), 4.60 (bs, 2H), 6.91 (s, 1H), 7.35-7.41 (m, 1H), 7.47-7.55 (m, 1H), 7.56-7.62 (m, 1H), 8.00-8.04 (m, 1H)
LC/MS (I) (5-90%, 5 min): 1.94, 464 (M+H).
Chiral separation (15:85:0, 0.7mL/min): 23.5 (E1); 39.7 (E2).

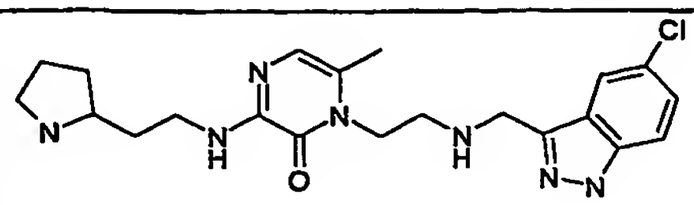
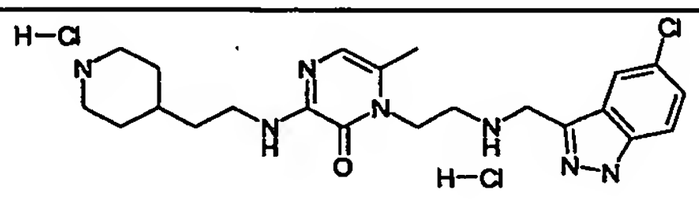
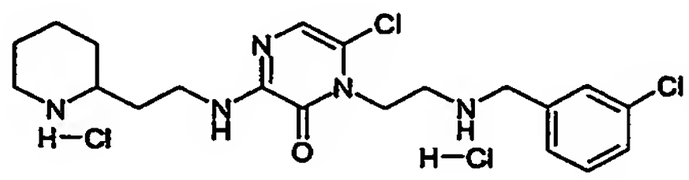
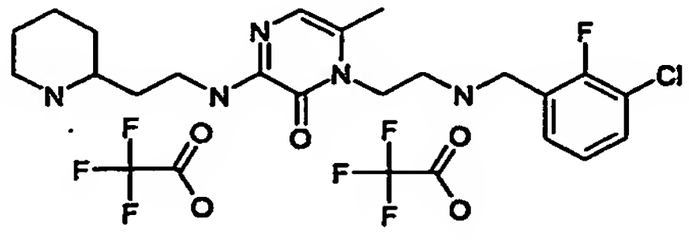
Following the procedure outlined for Example 101, the compounds listed in the Table 4 were prepared.

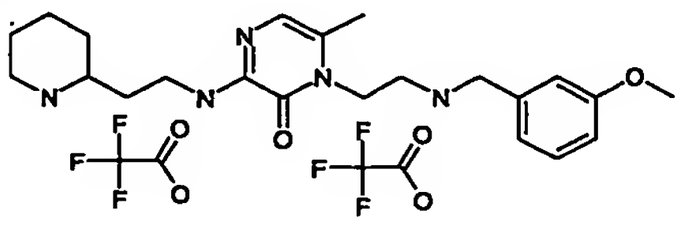
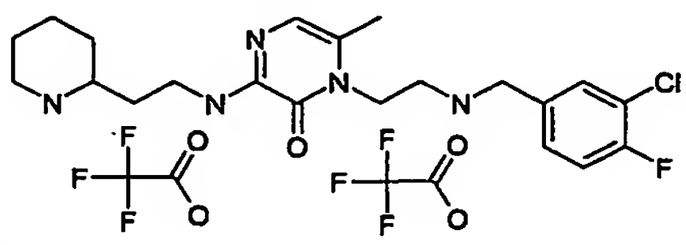
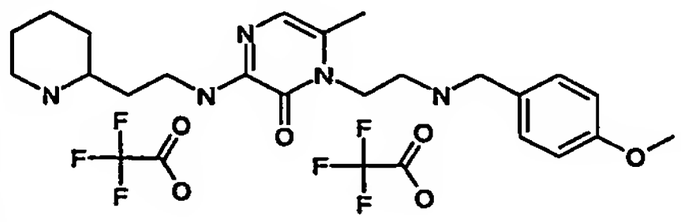
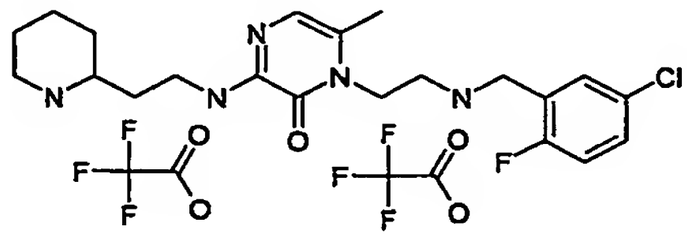
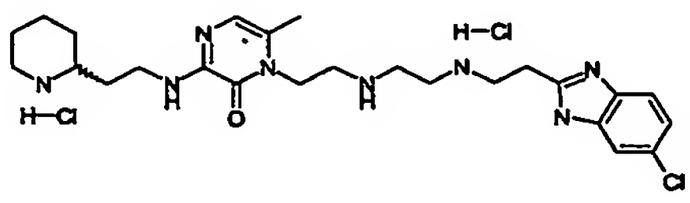
TABLE 4

Ex.	Structure	Selected ^{1}H-NMR data, (300 MHz) δ	LC/MS data (rt, m/z)

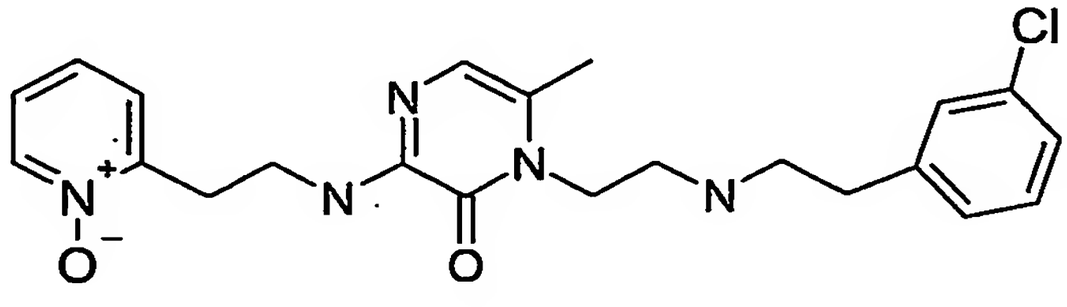
102		0.80-1.08 (m, 1H), 1.15-1.31 (m, 2H), 1.44-1.59 (m, 4H), 1.62-1.75 (m, 1H), 2.16 (m, 3H), 2.31-2.55 (m, 2H),2.68-2.72 (m, 2H), 2.81-2.94 (m, 1H), 3.19-3.37 (m, 2H), 3.69 (s, 2H), 3.85-3.96 (m, 2H), 6.54 (s, 1H), 6.71-6.84 (m, 1H), 7.13-7.36 (m, 4H)	(I) (5-95%, 10 min) 2.14 404 (M+H)
103		1.18-1.62 (m, 3H), 1.64-1.69 (m, 3H), 1.80-1.98 (m, 2H), 2.70-3.07 (m, 4H), 3.15-3.47 (m, 7H), 4.29-4.46 (m, 2H), 6.91 (s, 1H), 7.15-7.25 (m, 1H), 7.25-7.45 (m, 4H), 7.51-7.63 (m, 1H)	(I) (5-95%, 10 min) 2.48 418 (M+H)
104		0.96-1.08 (m, 1H), 1.17-1.33 (m, 2H), 1.40-1.58 (m, 4H) 1.62-1.75 (m, 1H), 2.14 (s, 3H), 2.32-2,49 (m, 4H), 2.74-2.78 (m, 2H), 2.85-2.89 (m, 1H), 3.92-3.97 (m, 2H), 4,00 (s, 2H), 6.53 (s, 1H), 6.71-6.75 (m, 1H), 7.25-7.28 (m, 1H), 7.43-7.46 (m, 1H), 7.85-7.86 (m, 1H)	(I) (5-90%, 5 min) 2.14 444 (M+H) chiral separation (15:85:0, 0.7mL/min): 14.07 (E1) 19.92 (E2)
105		1.18-1.62 (m, 3H), 1.64-1.79 (m, 3H), 1.80-1.98 (m, 2H), 2.70-3.07 (m, 4H), 3.15-3.47 (m, 7H), 4.29-4.46 (m, 2H), 6.91 (s, 1H), 7.15-7.25 (m, 1H), 7.25-	(I) (5-95%, 5 min) 1.95 438 (M+H)

		7.45 (m, 4H), 7.51-7.63 (m, 1H)	

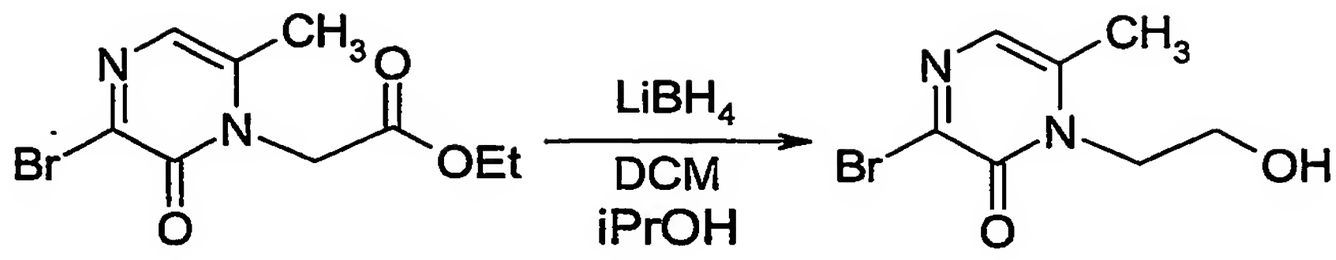
106		0.76-0.91 (m, 1H), 1.12-1.39 (m, 2H), 1.47-1.71 (m, 3H), 1.79-1.90 (m, 1H), 2.15 (s, 3H), 2.71-2.83 (m, 2H), 2.83-2.91 (m, 1H), 2.95-3.06 (m, 1H) 3.20-3.33 (m, 2H), 3.92-3.98 (m, 2H), 4.00 (s, 2H), 6.50-6.57 (m, 1H), 6.80-6.90 (m, 1H), 7.22-7.30 (m, 1H), 7.42-7.48 (m, 1H), 7.83-7.88 (m, 1H)	(I) (5-95%, 5 min) 1.67 430 (M+H) chiral separation (15:85:0, 0.7mL/min): 20.50 (E1) 27.35 (E2)
107		1.28-1.45 (m, 2H), 1.51-1.71 (m, 3H), 1.76-1.90 (m, 3H), 1.91 (s, 3H), 2.73-2.88 (m, 3H), 3.18-3.22 (m, 2H), 3.33 (bs, 2H), 4.30-4.35 (m, 2H), 4.58 (s, 2H), 6.64 (s, 1H), 7.37-7.45 (m, 1H), 7.60-7.77 (m, 1H), 8.16-8.25 (m, 1H)	(I) (10-90%, 5 min) 1.43 444 (M+H)
108		0.93-1.09 (m, 1H), 1.19-1.35 (m, 2H), 1.42-1.62 (m, 4H), 1.63-1.72 (m, 1H), 2.42-2.52 (m, 2H), 2.70-2.79 (m, 2H), 2.87-2.97 (m, 1H), 3.23-3.35 (m, 2H), 3.70 (s, 2H), 4.05-4.16 (m, 2H), 6.83 (s, 1H), 7.15-7.37 (m, 4H)	(I) (5-95%, 5 min) 1.68 424 (M+H) chiral separation (15:85:0, 0.7mL/min): 30.4 (E1), 31.9 (E2)
109			(I) (1-30%, 8 min) 5.22 422 (M+H)

110			(I) (1-30%, 8 min) 4.96 400 (M+H)
111			(I) (1-30%, 8 min) 5.53 422 (M+H)
112			(I) (1-30%, 8 min) 4.91 400 (M+H)
113		1.21-1.63 (m, 3H), 1.68-1.97 (m, 5H), 2.18 (s, 3H), 2.71-2.88 (m, 1H), 2.88-3.04 (m, 1H), 3.19-3.76 (m, 5H), 4.15-4.29 (m, 4H), 6.63 (s, 1H), 7.18 (m, 1H) 7.30-7.38 (m, 1H), 7.48-7.56 (m, 1H), 7.63-7.69 (m, 1H)	(I) (1-30%, 8 min) 4.43 422 (M+H)
114			(I) (5-95%, 5 min) 1.72 458 (M+H)

Example 115



Step 1

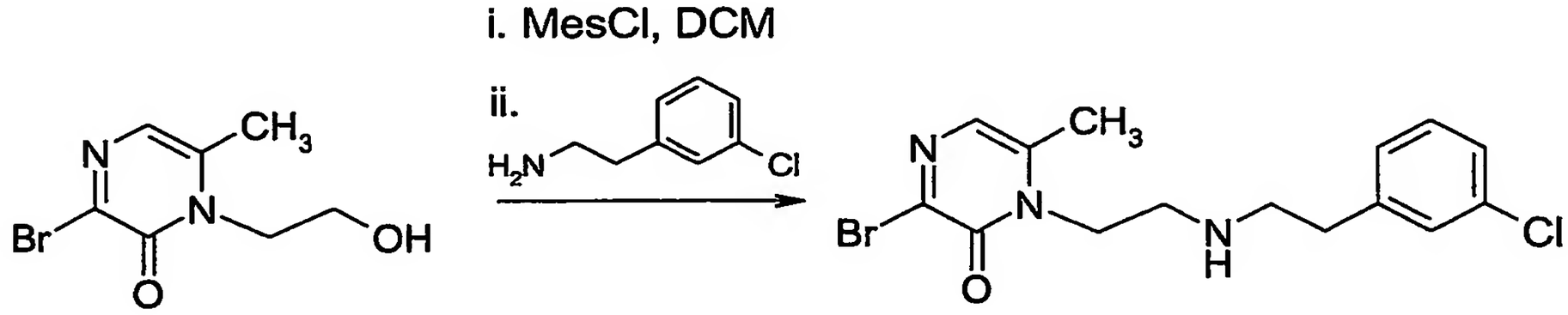


3-Bromo-1-(2-hydroxy-ethyl)-6-methyl-1H-pyrazin-2-one

(3-Bromo-6-methyl-2-oxo-2H-pyrazin-1-yl)-acetic acid ethyl ester (1100 mg, 4.00 mmol) is dissolved in dichloromethane (20 mL) and 2-propanol (5 mL) added under an argon atmosphere. The solution is cooled to 0 °C and 4 mL (4 mmol) of a 2 M solution of lithium borohydride in THF are added slowly. The solution is stirred at 0 °C for 20 min, then at room temperature for 2.5 h.

The reaction mixture is cooled to 0 °C and methanol is added until a clear solution is obtained after gas evolution is finished. 20 ml of pH 6 phosphate buffer are added and the biphasic mixture is allowed to warm to r.t. under vigorous stirring. The phases are separated and the aqueous layer is extracted with eight portions of ethyl acetate. The combined organic layers are dried over natrium sulfate and evaporated. The obtained crude product (745 mg, 80 %) is used in the next step without further purification.
LC/MS (I) (5-95%, 10 min): 1.54, 233 (M+H).

Step 2



3-Bromo-1-{2-[2-(3-chloro-phenyl)-ethylamino]-ethyl}-6-methyl-1H-pyrazin-2-one

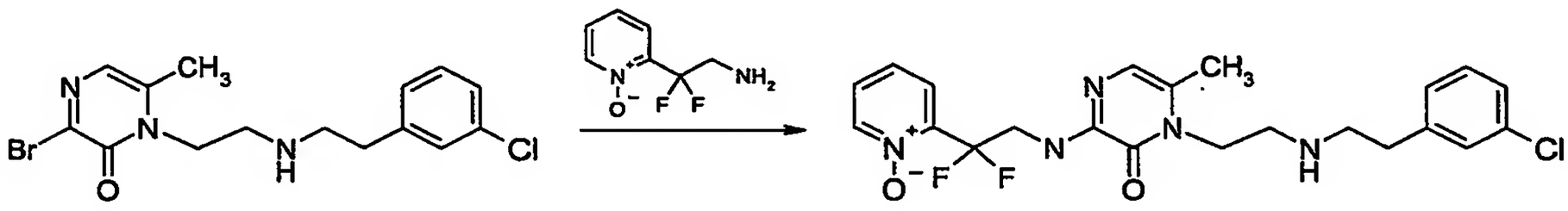
3-Bromo-1-(2-hydroxy-ethyl)-6-methyl-1H-pyrazin-2-one (340 mg, 1.46 mmol) is dissolved in dichloromethane (40 mL) and triethylamine (453 µl, 3.32 mmol) is added under an argon atmosphere. The reaction mixture is cooled to 0 °C and a solution of methanesulfonylchloride (180 µl, 2.33 mmol) in 1 mL of dichloromethane is added slowly. Stirring at 0 °C is continued for 60 min. At 0 °C methanol (2 mL) is added and

the reaction mixture is washed with pH 6 phosphate buffer, saturated sodium bicarbonate solution and brine. After drying over sodium sulfate the organic phase is evaporated.

The remaining residue is taken up in 15 mL acetonitrile and added dropwise to a solution of 2-(3-chlorophenyl)-ethylamine (382 µL, 2.75 mmol) in acetonitrile (15 mL). The mixture is warmed to 55 °C for 2 h. The mixture is concentrated and the residue is adsorbed on amino functionalized silica gel (Flash NH2, IST ltd., UK). Chromatography on silica gel (0 % to 10 % methanol in dichloromethane) affords 358 mg (89 %) of the title compound.

LC/MS (I) (5-95%, 10 min): 2.02, 372 (M+H).

Step 3



1-{2-[2-(3-Chloro-phenyl)-ethylamino]-ethyl}-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-6-methyl-1H-pyrazin-2-one

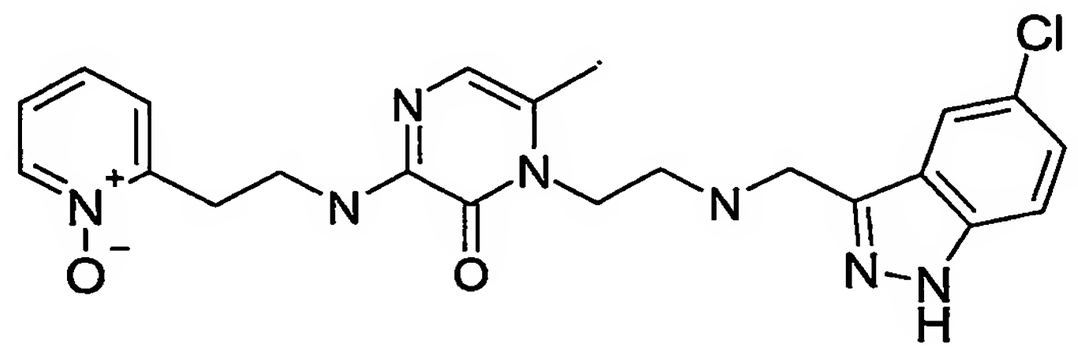
3-Bromo-1-{2-[2-(3-chloro-phenyl)-ethylamino]-ethyl}-6-methyl-1H-pyrazin-2-one 2 (67 mg, 181 µmol), 2-mercaptopyridine (12 mg, 108 µmol) and 2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamine (96 mg, 551 µmol) are dissolved in acetonitrile (1.5 mL) under an argon atmosphere. A solution of zinc(II) chloride in DCM (0.73 M, 136 µL, 100 µmol) is added under stirring and the resulting mixture is heated to 125 °C in a sealed tube for 48 h.

After cooling to r.t. the reaction mixture is filtered through silica gel. The silica gel is first rinsed with acetonitrile (50 mL), then with dichloromethane/methanol (8:2 v/v, 50 mL). The fraction from the dichloromethane/methanol rinsing is evaporated and taken up in dichloromethane/methanol (10 mL). The resulting suspension is filtered through a PTFE syringe filter and evaporated. Purification by preparative LCMS (water/acetonitrile/TFA gradient) affords 21.7 mg (17 % yield) of the title compound as the bis-TFA salt.

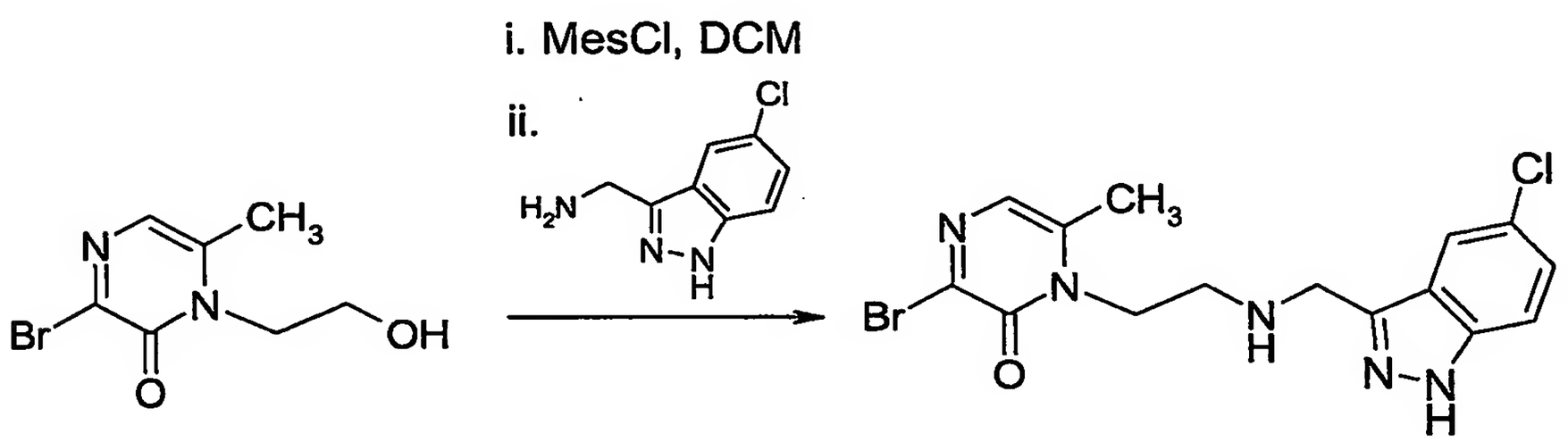
^{1}H-NMR (300 MHz) δ = 2.15 (s, 3H), 2.86-2.94 (m, 2H), 3.22 (bs, 2 H), 4.11-4.19 (m, 2 H), 4.37-4.50 (m, 2 H), 6.53 (s, 1 H), 6.96-7.03 (m, 1 H), 7.16-7.20 (m, 1 H), 7.26-7.40 (m, 2 H), 7.47-7.61 (m, 2 H), 8.28-8.33 (m, 1H), 8.69 (bs, 2 H)

LC/MS (I) (5-95%, 10 min): 2.77, 464 (M+H).

Example 116



Step 1



<u>3-Bromo-1-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-6-methyl-1H-pyrazin-2-one</u>

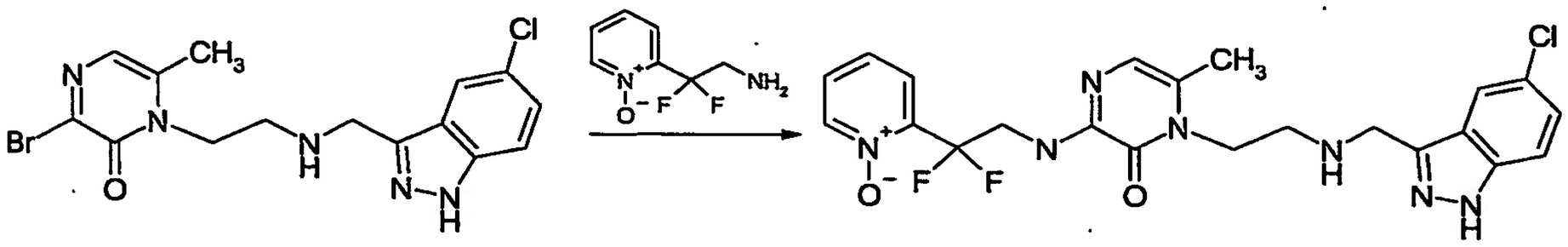
3-Bromo-1-(2-hydroxy-ethyl)-6-methyl-1H-pyrazin-2-one (60 mg, 258 µmol) is dissolved in dichloromethane (8 mL) and triethylamine (87 µL, 622 µmol) is added under an argon atmosphere. The reaction mixture is cooled to 0 °C and a solution of methanesulfonylchloride (35 µl, 452 µmol) in 1 ml of dichloromethane is added slowly. Stirring at 0 °C is continued for 60 min. At 0 °C methanol (2 ml) is added and the reaction mixture is washed with pH 6 phosphate buffer, saturated sodium bicarbonate solution and brine. After drying over sodium sulfate the organic layer is evaporated.

The residue is taken up in 3 mL acetonitrile and added dropwise to a solution of C-(5-chloro-1H-indazol-3-yl)-methylamine (120 mg, 661 µmmol) in acetonitrile (3 mL). The mixture is warmed to 55 °C for 5h. The mixture is concentrated and the residue is adsorbed on amino functionalized silica gel (Flash NH_2, IST ltd., UK). Chromatography

on silica gel (0 % to 10 % methanol in dichloromethane) affords 94 mg (91 %) of the title compound.

LC/MS (I) (5-95%, 10 min): 2.07, 398 (M+H).

Step 2



1-{2-[(5-Chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-6-methyl-1H-pyrazin-2-one

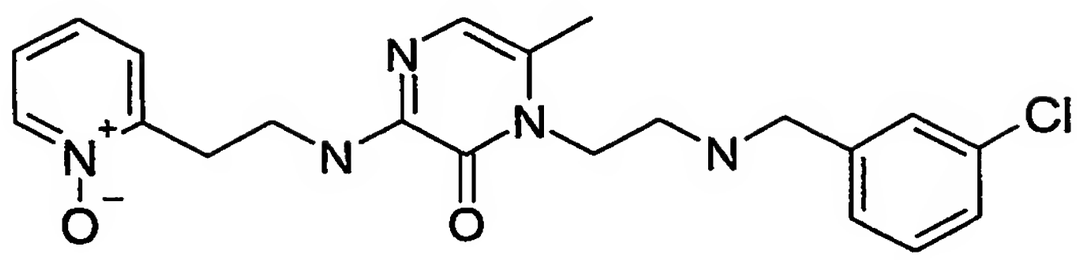
3-Bromo-1-{2-[(5-chloro-1H-indazol-3-ylmethyl)-amino]-ethyl}-6-methyl-1H-pyrazin-2-one 3 (70 mg, 176 µmol)), 2-mercaptopyridine (12 mg, 108 µmol) and 2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamine (110 mg, 631 µmol) are dissolved in acetonitrile (1.5 mL) under an argon atmosphere. A solution of zinc(II) chloride in DCM (0.73 M, 136 µL, 100 µmol) is added under stirring and the resulting mixture is heated to 85 °C in a sealed tube for 27 h.

After cooling to room temperature the reaction mixture is filtered through silica gel. The silica gel is first rinsed with acetonitrile (50 mL), then with dichloromethane/methanol (8:2 v/v, 100 mL). The fraction from the dichloromethane/methanol rinsing is evaporated and taken up in dichloromethane/methanol (10 mL). The resulting suspension is filtered through a PTFE syringe filter and evaporated. Purification by preparative LCMS (water/acetonitrile/TFA gradient) affords 26.4mg (20 % yield) of the title compound as the bis-TFA salt.

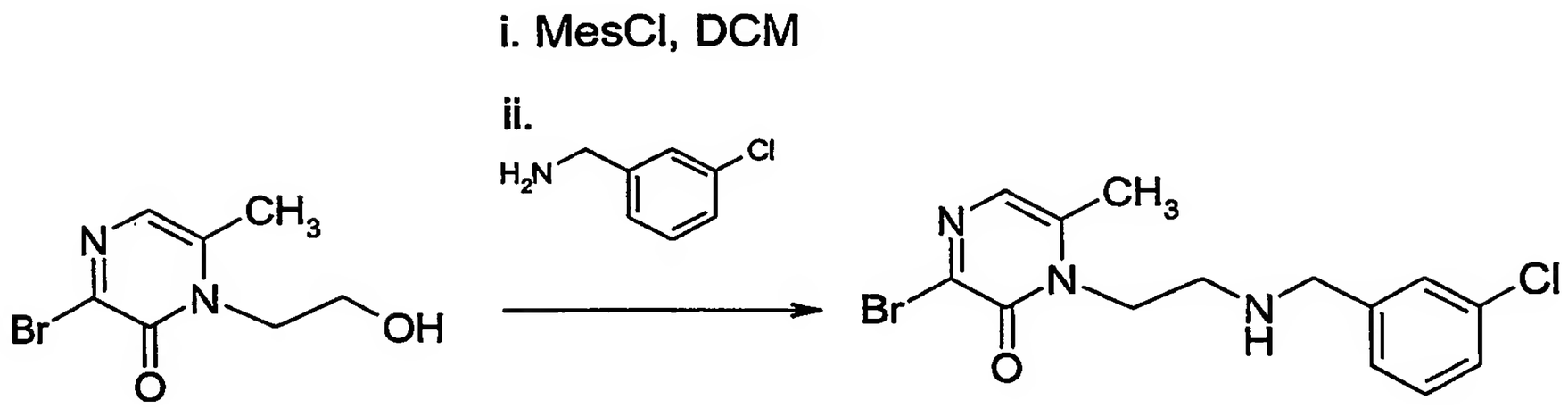
^{1}H-NMR (300 MHz) δ = 2.16 (s, 3 H), 3.34 (bs, 2H), 4.17-4.24 (m, 2H), 4.36-4.50 (m, 2H), 4.56 (bs, 2H), 6.52 (s, 1H), 6.94-7.02 (m, 1H), 7.31-7.42 (m, 2H), 7.46-7.61 (m, 3H), 8.02-8.04 (m, 1H), 8.28-8.32 (m, 1H), 9.15 (bs, 2H), 13.52 (bs, 1H).

LC/MS (I) (5-95%, 10 min): 3.25, 490 (M+H).

Example 117



Step 1



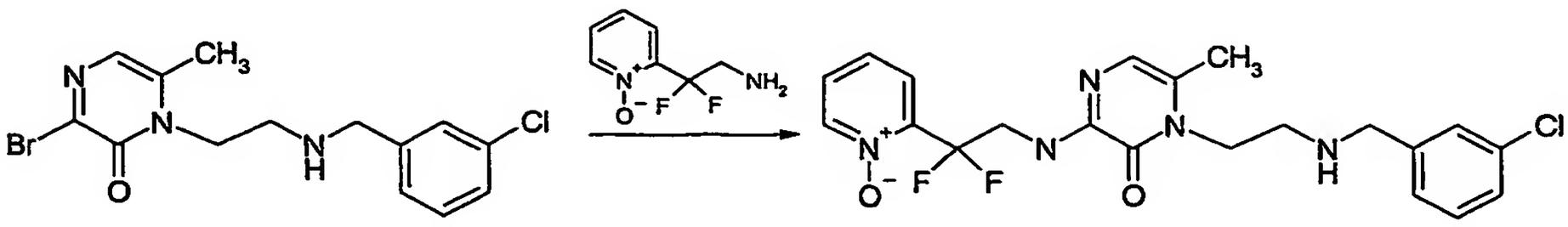
3-Bromo-1-[2-(3-chloro-benzylamino)-ethyl]-6-methyl-1H-pyrazin-2-one

1 (100 mg, 430 µmol) is dissolved in dichloromethane (13 mL) and triethylamine (145 µl, 1.04 mmol) is added under an argon atmosphere. The reaction mixture is cooled to 0 °C and a solution of methanesulfonylchloride (58 µl, 753 µmol) in 1 mL of dichloromethane is added slowly. Stirring at 0 °C is continued for 60 min. At 0 °C methanol (2 mL) is added and the reaction mixture is washed with pH 6 phosphate buffer, saturated sodium bicarbonate solution and brine. After drying over sodium sulfate the organic layer is evaporated.

The residue is taken up in 3 mL acetonitrile and added dropwise to a solution of 3-chlorobenzylamine (131 µL, 1.07 µmmol) in acetonitrile (3 mL). The mixture is warmed to 60 °C for 5h. The mixture is concentrated and the residue chromatographed on silica gel (0 % to 10 % methanol in dichloromethane). Thus, 100 mg (84 %) of the title compound are obtained.

^{1}H-NMR (300 MHz) δ = 2.34 (s, 3H), 2.76 (t, 2 H), 3.25 (bs, 1 H), 3.68 (s, 2 H), 4.02 (t, 2 H), 7.05 (s, 1 H), 7.13-7.29 (m, 4 H)
LC/MS (I) (5-95%, 10 min): 2.75, 258 (M+H).

Step 2



1-[2-(3-Chloro-benzylamino)-ethyl]-3-[2,2-difluoro-2-(1-oxy-pyridin-2-yl)-ethylamino]-6-methyl-1H-pyrazin-2-one

Obtained from 3-bromo-1-[2-(3-chloro-benzylamino)-ethyl]-6-methyl-1H-pyrazin-2-one according to the procedure described for Step 2 in Example 116.

^{1}H-NMR (300 MHz) δ = 2.14 (s, 3H), 3.13-3.30 (m, 2 H), 4.09-4.25 (m, 4 H), 4.32-4.57 (m, 2 H), 6.53 (s, 1 H), 6.99-7.14 (m, 1 H), 7.29-7.63 (m, 7 H), 8.29-8.31 (m, 1H).

ASSAYS

Example 118 aPTT protocol

The aPTT measurements were carried out with an CoaData coagulometer from HelenaBioscience on 50 µl human standard plasma obtained from Dade Behring. After activation with 50 µl ellagic acid and cephalin using the Actin kit from Dade Behring, coagulation was triggered by addition of 50 µl 25mM calcium chloride. Clotting time was measured by the instrument in seconds.

Example 119 K_i determinations thrombin

The Ki determinations were carried out at 20 °C with the fluorogenic substrate Tosyl-GPR-AMC (Bachem, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at a thrombin concentration of 100 pM in HBS pH 7.4. The substrate was added to a final concentration of 20 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were

estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

HBS: 10 mM Hepes, 150 mM NaCl, 0.005 % Tween20, pH 7.4

Example 120 Protease assays

Factor Xa:

The Ki determinations were carried out at 20 °C with the fluorogenic substrate Boc-LGR-AMC (Bachem, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at a fXa concentration of 1 nM in HBS pH 7.4, 5 mM calcium chloride. The substrate was added to a final concentration of 100 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

HBS: 10 mM Hepes, 150 mM NaCl, 0.005 % Tween20, pH 7.4

Tryptase:

The Ki determinations were carried out at 20 °C with the fluorogenic substrate Boc-FSR-AMC (Bachem, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at a Tryptase concentration of 1 nM in HBS pH 7. The substrate was added to a final concentration of 20 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

HBS: 10 mM Hepes, 150 mM NaCl, 0.005 % Tween20, pH 7

Trpysin:

The Ki determinations were carried out at 20 °C with the fluorogenic substrate Z-GGR-AMC (Bachem, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at a Trypsin concentration of 0.001 U/ml in TBS pH 8. The substrate was added to a final concentration of 100 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

TBS: 20 mM Tris, 150 mM NaCl, 0.005 % Tween20, pH 8

Chymotrpysin:

The Ki determinations were carried out at 20 °C with the fluorogenic substrate H-AAF-AMC (Bachem, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at a Chymotrpysin concentration of 1 nM in TBS pH 8. The substrate was added to a final concentration of 100 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

TBS: 20 mM Tris, 150 mM NaCl, 0.005 % Tween20, pH 8

Elastase

The Ki determinations were carried out at 20 °C with the fluorogenic substrate MeOSuc-AAPV-AMC (Loxo, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at an Elastase concentration of 5 nM in Hepes buffer pH 7. The substrate was added to a final concentration of 100 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were

estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

Hepes buffer: 10 mM Hepes, 50 mM NaCl, 0.005 % Tween20, pH 7

Plasmin

The Ki determinations were carried out at 20 °C with the fluorogenic substrate H-D-ALK-AMC (Bachem, Heidelberg, Germany; λ_{exc} = 370 nm, λ_{em} = 450 nm) at a plasmin concentration of 1 nM in HBS pH 7.4, 5 mM calcium chloride. The substrate was added to a final concentration of 100 µM in a total assay volume of 100 µl. The enzymatic reaction was started by addition of substrate. The emission at 450 nm was monitored in 1 minute intervals for 10 minutes using a polarstar reader (BMG Laboratories, Offenburg, Germany). Initial velocities of the control and the inhibited reactions (v_o and v_i) were estimated in FU/min at different compound concentrations. The inhibition constants were calculated using the Michaelis-Menten equation for competitive inhibition.

HBS: 10 mM Hepes, 150 mM NaCl, 0.005 % Tween20, pH 7.4

Example 121 Selectivity profile

Table 3 lists K_i values for related proteases determined in assays as described in example 120 for 16 compounds and demonstrate the high degree of selectivity for the inhibition of thrombin compared to the other related proteases.

The Ki values were grouped in 3 classes: a means ≤ 200 nM; b means ≤ 30 nM and C means ≤ 5 nM.

The data were grouped in 3 classes: A means an increase of 1000 to 10000 folds respect to the Ki value; B means an increase of >10000 to 10^6 folds and C means >10^6 folds.

Example	Ki (μM) Thrombin	Ki (μM) factorXa	Ki (μM) Plasmin	Ki (μM) Tryptase	Ki (μM) Trypsin	Ki (μM) Elastase	Ki (μM) Chymotrypsin	Ki (μM) aPC	Ki (μM) Kallikrein	Ki (μM) tPA
84	b	A	B	B	B	B	B	B	B	B
85 (E1)	c	B	C	C	B	C	A	C	B	C
101 (E2)	c	A	B	B	B	B	A	B	B	B
74	c	B	B	B	B	B	A	B	B	B
82	c	B	C	C	C	C	B	C	C	C
95 (E2)	c	A	B	B	B	B	A	B	B	B
96	b	A	B	B	B	B	A	B	B	B
83	c	A	B	B	B	B	B	B	B	B
97	c	A	B	B	B	B	A	B	B	B
95 (E1)	c	B	B	B	B	B	B	B	B	B
52	a	A	B	B	B	A	B			
99	a	A	B	B	B	B	A			
56	a	A	A	A	A	A	A			
59	a	A	A	A	A	A	A			
92	c	B	B	B	B	B	B			
102	b	A	B	B	B	B	B			

TABLE 3